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Surgical pathology in cancer diagnosis: implications for quaternary prevention

Anatomia patológica no diagnóstico do câncer: implicações para a prevenção quaternária

Patología quirúrgica en el diagnóstico de cáncer: implicaciones para la prevención cuaternaria

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Abstract

Surgical pathology is the medical specialty in charge of cancer diagnosis. Although very important since oncology development, its link with overdiagnosis and overtreatment remains understudied. Despite big mediatisation, molecular biology has not brought much progress to tumour classifications. On the contrary, the silent apparition of immunohistochemistry at the end of the 1980's improved much of tumour classifications so significantly that it could cast doubts in some trials' results of that period. This article discusses how the booming and abuse of immunohistochemistry might have led to overdiagnosis. It also highlights that the ISO 15189 standardization, as well as the tumour classification complexity, might function to induce overtreatment. In summary, critical reading and understanding of pathology reports by general practitioners are essential. Therefore, family doctors should not hesitate to discuss the cancer diagnosis with the pathologist, and in some cases also question the oncologist decision. This approach can be considered a quaternary prevention action which can prevent overtreatment.

Keywords:
Quaternary Prevention
Pathology, Surgical
Uterine Cervical Neoplasms

Resumo

A anatomia patológica é a especialidade médica responsável pelo diagnóstico de câncer. Apesar de muito importante, a partir do desenvolvimento da oncologia, sua ligação com o sobrediagnóstico e sobretratamento permanece ainda pouco estudada. Apesar de grande midiatização, a biologia molecular não trouxe muito progresso para a classificação dos tumores. Ao contrário, a aparição silenciosa de imunohistoquímica, no final da década de 1980, foi o que melhorou significativamente as classificações tumorais, a ponto de ser possível lançar dúvidas sobre os resultados de alguns ensaios clínicos desse período. Este artigo discute como o auge e o abuso da imunohistoquímica pode ter levado ao sobrediagnóstico. Ele também destaca que a padronização ISO 15189, assim como a complexidade de classificação tumoral, podem também contribuir para a indução do sobretratamento. Em suma, a leitura crítica e a compreensão dos laudos de patologia por parte dos médicos de família são essenciais. Portanto, os médicos de família não deveriam hesitar em discutir o diagnóstico de câncer com o patologista e, em alguns casos, também questionar a decisão do oncologista. Essa abordagem pode ser considerada uma ação de prevenção quaternária que pode prevenir o sobretratamento.

Palavras-chave:
Prevenção Quaternária
Patologia Cirúrgica
Neoplasias do Colo do Útero

Resumen

La patología quirúrgica es la especialidad médica encargada del diagnóstico de cáncer. Aunque es muy importante, desde el desarrollo de la oncología, su vínculo con el sobrediagnóstico y sobretratamiento sigue pendiente de estudio. A pesar de gran mediatización, la biología molecular no ha traído mucho progreso para las clasificaciones tumorales. Por el contrario, la aparición silenciosa de la inmunohistoquímica, en el final de la década de 1980, mejoró mucho las clasificaciones tumorales, a punto de que sea posible plantear dudas sobre los resultados de algunos ensayos clínicos en ese período. Este artículo describe cómo el auge y el abuso de la inmunohistoquímica puede tener llevado al sobrediagnóstico. También destaca que la estandarización ISO 15189, así como la complejidad de la clasificación tumoral, pueden también contribuir para la inducción del sobretratamiento. En suma, la lectura crítica y la comprensión de los informes de patología por los médicos familiares son esenciales. Portanto, los médicos de familia no deberían vacilar en discutir el diagnóstico de cáncer con el patólogo y, en algunos casos, también cuestionar la decisión del oncólogo. Este enfoque puede ser considerado una acción de prevención cuaternaria que puede prevenir el sobretratamiento.

Palabras clave:
Prevención Cuaternaria
Patología Quirúrgica
Neoplasias del Cuello Uterino

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Background: the boom of immunohistochemistry

Surgical pathology is a huge but hidden specialty. Modern pathology using the microscope began with Rudolf Virchow,[1] a XIX century German doctor and professor. Juan Rosai[2] describing the beginning of pathology in the United States of America refers to it as a surgical and mainly experimental specialty. The first residents of surgical pathology appear in the 1940's. Pathology grew much after World War II, leaving behind its surgical component to become an independent laboratory department in the 1960s. Up to 1960, surgical pathology used only light microscope and stains (histochemistry).[3] Electron microscopy was used in the middle of the XX century, but was abandoned in the eighties due to the advent of immunohistochemistry.

Immunohistochemistry uses a small amount of animal antibodies to mark cells and help tumour typing. Between 1980 and 2000 immunohistochemistry boomed with pathology laboratories being progressively equipped with these techniques. Around 2000, Ventana Medical Systems[4] released the first immunohistochemistry automates.[5] Thus, immunohistochemistry has become easier and quicker to perform. Immunohistochemistry has ascertained its important role on pathology diagnosis and has not yet been championed. For instance, molecular biology, though very mediated, is only performed in a few cases after light microscopy and immunohistochemistry, to complete the diagnosis process.

Hence, interesting would be to find out if pathology can be linked to overdiagnosis and overtreatment since it has been recently reported some controversies over screening programmes,[6] as well as in cancer overdiagnosis.[7] The rationale for that is that screening programmes may identify a reservoir of indolent tumours. These are not life-threatening conditions, and potentially can lead to overdiagnosis and overtreatment.[8] For this reason, it has been suggested a need for changing cancer terminology. The term 'cancer' should be reserved for describing lesions with a reasonable likelihood of lethal progression, if left untreated.[9] This would be the first step in understanding and mapping the overdiagnosis phenomenon.

The current literature on overdiagnosis did not investigate much in surgical pathology. The researchers have been looking to overdiagnosis, mostly from epidemiological perspective, with little emphasis on surgical pathology. Thus, it might be interesting to explore how pathology can be an overdiagnosis accomplice and actor. This article emphasises the limits and future of pathology and the so called 'technological progresses' suggesting that family physicians could have a role in dealing with pathological reports as an action for quaternary prevention.

Before the spread of immunohistochemistry in the 1990's: an unknown amount of cancer misclassified

Immunohistochemistry uses antibodies to mark cells and at first the technique was manual, quite difficult to handle, and time consuming. In pathology, one antibody is rarely used alone. For instance, after screening the case on the microscope, the pathologist can use a panel of antibodies to make the diagnosis. This whole process was revolutionised 15 years ago with Ventana medical system, which for the first time has automatized the immunohistochemistry process.[5] This favoured its expansion and confirmed its success. As a result, some traditional stains in tumour typing were abandoned or replaced by immunohistochemistry.

For example, in endocrine tumour diagnosis, the use of Grimelius stain was phased out by immunohistochemistry and the use of synaptophysin and chromogranin is now clearly acknowledged. With the introduction of immunohistochemical techniques, tumours could be characterized in a more specific way regarding peptide hormones and biogenic amines content,[6] but no publication has been found ascertaining the definite superiority of immunohistochemistry against Grimelius stain. In 1992, Cetin[10] still recommended to perform Grimelius stain. Currently, in Western countries, Grimelius stain has been completely abandoned and not even pathology textbooks refer to it anymore.

In 1985, Gatter et al.[11] from Oxford University, highly recommended the brand new immunohistochemistry methods in tumour diagnosis since undifferentiated carcinoma cases diagnosed by light microscopy alone ("old" pathologic diagnosis prior to 1980-1990) were reviewed and examined with new immunohistochemistry methods. Half of the 'carcinoma' cases have been reclassified in lymphoma, which is opposite to carcinoma, 'curable' with adequate chemotherapy. Gatter et al.[11] urged pathologists to use immunohistochemistry: *'Immunohistological methods can now resolve the majority of difficulties arising over the histological diagnosis of malignant tumours, and these methods should, therefore, be used on a wide scale by diagnostic histopathology laboratories'*.

Hence, Gatter et al. have demonstrated that immunohistochemistry helps the pathologists to classify tumours and that without the advent of immunohistochemistry, big mistakes have been made. Their assertiveness was based on the misclassification of lymphomas, which previously to immunohistochemistry techniques were diagnosed as carcinomas. In other words, if the patients were diagnosed as having carcinoma, they might have not started chemotherapy, which could have cured them. Gatter et al.'s message was very important because in 1985 just few laboratories were performing immunohistochemistry.

Immunohistochemistry side effects: useless antibodies

Immunohistochemistry was at first a great help to the pathologist diagnosis, but the antibodies manufacturers boomed and underwent aggressive marketing campaigns. The P16 protein is the typical antibody, whose campaign has been described as 'aggressive' by some scientists.[12] This abuse of antibodies is not trivial. For instance, in case of doubt between 'normal' or dysplasia in cervix biopsy, P16 immunohistochemistry might be helpful.[13] However, the same P16 might be used for dysplasia grading, which presumably induces overdiagnosis of high-grade dysplasia.[14] A diagnosis of high-grade dysplasia is not a banal thing, since it involves resection of cervix as treatment (conisation), which has implications for subsequent deliveries.[15] According to Carrigg and Hasteh[16] from UC San Diego health system, 17% of conisations are normal and, therefore, unjustified. In other words, as result of Pap smear screening for cervical cancer, nearly one out five women would have her normal cervix being taken off, increasing her chances of having a premature delivery.

Ventana, Roche and ISO 15189

Ventana is a big corporation which only deals with pathologists. Ventana does not only sell machines, it also sells antibodies that can work with its automated devices. Additionally, Ventana automates also work with other corporation antibodies. Ventana also invented and sold around the year 2000 the first automate which could perform the whole immunohistochemistry technique by itself. It was a huge success and Ventana took the first rank in the world immunohistochemistry market: in 2011, in the US, it had more than 50% of the immunohistochemistry $650 million market.[13] In 1998, the US Food & Drug Administration approved Roche's Herceptin (trastuzumab) as a chemotherapy drug for breast cancer. To be prescribed, Herceptin needs an associated test, the HER-2 immunohistochemistry test. If enough cells are marked by the HER-2, then Herceptin can be prescribed. Around 15% of the breast cancers are positive for HER-2 tests. In order to prescribe Roche's Herceptin, oncologists must have a positive HER-2 test. It is made on the breast cancer slides by pathologists by means of immunohistochemistry.

The CAP-ASCO (College of American Pathologists-American Society of Clinical Oncology) recommendations for HER-2 test interpretation changed 3 times since its birth.[17] Before 2007, it was positive if more than 10% of the cells were strongly stained. From 2007 onwards the requirement increased to up 30%. Recently, in 2014, it was dragged back to 10%. The FISH interpretation levels have also changed in the same period. In 2014, one of the most important pathology review study noticed that '*Certain recommendations, particularly those related to repeating the test and pathological concordance, have lower levels of supportive evidence than existing key recommendations*".[16] This recent HER-2 test cut-off change may increase Herceptin prescription for the years to come. Since Ventana's acquisition by Roche, in 2008, for the cost of 3,4 billion dollars,[18] Roche controls now all the pathology diagnosis pathway: the Ventana HER-2 antibody, the Ventana immunohistochemistry automate and the Herceptin drug. Thus, currently Roche sells the companion test and the drug as well.

The new world standard ISO 15189, which is based on ISO 9001 quality management system is now applied to medical biology laboratories. It has become mandatory for medical biology in a few countries,[19] especially France and Belgium, although it is not mandatory in the USA.[20] It is also beginning to be applied to some surgical pathology laboratories. ISO 15189 states that the integrated systems should be preferred and most laboratories, which own Ventana automates, will be pushed to buy Ventana antibodies, in case of ISO 15189 being strictly applied.

Classification changes

The veracity of pathology diagnosis depends little on technique. It mainly depends on the pathologist's knowledge and skills and not everyone have the same level of dexterity. The pathology diagnosis is not infallible and thereby the inter-observer reproducibility is sometimes not satisfactory.[21] This would be improved by simple classifications, whose therapeutic benefits and reproducibility could be tested. Unfortunately this is not the trend, since WHO Classifications of tumours are determined by a small circle of 'experts' meetings, without much preliminary studies.[22] In addition, instead of releasing a mature classification every 20 years, the pace has been accelerated and classificatory criteria change more rapidly. However, as quoted in 2002, the 1998 WHO bladder tumour classification criteria are not better than the 1973, which is still widely used.[23] There are even some guidelines mistakes as the WHO/RENATEN 2010 classification of endocrine digestive tumour in which difference in methods could reach 44% of discordance.[24]

Discussion

The immunohistochemistry techniques which appeared in the eighties, as mentioned previously, were a big advance in pathology. It allowed making a more adequate diagnosis in a significant number of cases. Few publications reviewed the cases diagnosed before the existence of immunochemistry. The real impact of immunohistochemistry on the pathology diagnosis accuracy is difficult to estimate as already discussed above in The Lancet's seminal article.[11] It could be objected that this one paper is not enough to assert the value of immunohistological methods impact on tumour diagnosis. But, this is not the case because, certainly, before immunohistochemistry a significant amount of cancers was misclassified. Before the 1990's, pathologists might have misclassified tumours as carcinoma instead of lymphoma or melanoma. It was the technical limitation of that time and not the pathologists' fault. Although every senior pathologist admits now that immunohistochemistry was a big step forward, there is little interest in the period before immunohistochemistry in searching for classification discrepancies. If not, new review studies could be performed, since slides or paraffin blocks are stored for long time, which makes possible to review the 1970-1990 cases. This context is highlighted on the British Pathology Association website 'conversation with pathologists', where it is possible to listen to pathologist David A. Levison,[25] editor of a pathology textbook:

> *'Immunohistochemistry has made a huge difference. Before we had this, if we saw a mass of malignant cells, we could tell it was a tumour, but not definitely if it was a lymphoma, which is treatable, curable; or if it was an undifferentiated carcinoma which virtually nothing will touch, will kill you in a few weeks or months; or if it was a sarcoma for which there might be some other specific treatment. Now, with immunohistochemistry and the molecular techniques as well, we can tell in almost every case, "Yes that's a lymphoma, it's a B-cell lymphoma, usually curable. The chances are that 90% of people who have this sort of tumour will be still alive in five years, if they are treated with this particular regime'*.[25]

The only thing which is not accurate in this statement is that the old school of pathologists actually made a definite diagnosis, and misclassified tumours. Pathologists at that time did not know their limits as they were unknown to immunohistochemistry. They did not classify all those tumours as 'unclassified' or as 'undifferentiated tumours' as might be expected. In the 1985 Gatter et al. study[11] it was documented that 60% of the cases diagnosed as undifferentiated carcinoma were, after immunohistochemistry analysis, classified finally as lymphoma, which are curable entities. These facts are sufficient to suspect the occurrence of major biases results in some of the clinical chemotherapy trials of that time. Thus, old clinical trials based on pathology diagnosis and published with no or insufficient immunohistochemistry might be biased by tumour misclassification. The drug approvals based on those misclassified cases might then be ineffective. This is all the more accurate in sarcoma and also in bronchial carcinoma, melanoma, and lymphoma, which are not diagnosed now without immunohistochemistry and it is the less accurate in colonic adenocarcinoma that does not usually need immunohistochemistry for diagnosis.

On the one hand, immunohistochemistry is of great help for the pathologists, on the other hand it is being now so common that it might be overused. Immunohistochemistry overuse can hardly be contradicted. For instance, in 2012, a paper from the Department of Pathology, University of Virginia Health System[26] states:

> *'With its proliferation in pathology practice settings of all types, the temptation to overuse it [immunochemistry] continues. Immunochemistry should, of course, complement and not supersede information gleaned from the clinical context and the H & E-stained morphologic appearance. The pathology literature is inundated with articles that address the usefulness of diagnostic IHC [immunohistochemistry] algorithms and panels for tumour classification. However, there is a paucity of studies examining the patterns of usage of IHC among pathologists, possibly because of the inherent bias likely to be present in the study design'.*

The link between immunohistochemistry overuse and overdiagnosis is not yet proved, but highly suspected. In 1997, uropathologist Epstein emphasized that the percentage of minute cancer among prostatectomy has increased since PSA screening.[27] His remark on minute cancer, a cancer less than 7mm, is a reference that this prostate 'cancers' might be harmless. The overdiagnosis due to prostate screening has been proved by epidemiological studies.[28] Pathology might be a major cause of this overdiagnosis, but few pathologists have written about it. Epstein's article mentions PSA screening as a possible cause of overdiagnosis, but forgets to acknowledge the immunohistochemistry technique as playing also a major role in prostate cancer overdiagnosis. Nowadays, for almost 10 years, active surveillance for minimal prostate cancer (<1mm on biopsy) is quite advised and commonly accepted.[29]

Even though molecular biology knowledge has stepped forward, it does not help much the clinician to diagnose and treat cancer. Associated tests are now numerous (Braf, Kras mutations) as in the case of Thyrosine Kinase Inhibitors (approved by FDA) which are now more than twenty. They are mostly made by molecular biology (PCR), but previous diagnosis would have required only haematoxylin and eosin (H & E) coloration and perhaps, immunohistochemistry.

Pathology diagnosis demands experience more than technology. As Juan Rosai,[2] one of the most influential twentieth century pathologist has stated: *'despite all the advances in molecular biology and other disciplines, the diagnosis of solid tumours today is still based in the overwhelming majority of the cases on what we see under the microscope'.*[2]

Radiology is supported by manufacturers which sell big and expensive machines. Pathology does not need any expensive material. Cost effective analyses of surgical pathology has rarely been studied, but is very low,[30] or at least, lower than radiology, though it makes the definite diagnosis.

False advances in the area of pathology are focusing on useless features. For instance, ISO 15189 would not make pathologists to progress, but to divert the focus on trivial details, such as room or fridge temperature. This approach will not improve the quality of the diagnosis. However, if accreditation on ISO 15189 is applied worldwide to pathologists, it will not improve the accurate diagnosis, but it is likely to transform friendly familial pathology laboratory into a big diagnosis industrial manufacture to be launched in the stock exchange market. These transformations could be detrimental for surgical pathology efficiency. A skilled and committed pathologist tends to phone clinicians when there is a lack of clinical details, an essential step for making the diagnosis. The same slide image can be of a melanoma, if the patient is an adult, or a congenital *naevus* in the case of a newborn! Moreover, the industrialization of pathology might induce overdiagnosis, backed by pharmaceutical industry concerned with a positive association of immunohistochemical test to treat patients.

Conclusion

Surgical pathology is the key to cancer diagnosis and its role on overdiagnosis and overtreatment is underestimated. This article tries to point out the major overdiagnosis factors in surgical pathology. An unknown number of major tumour misclassification has been made before the emergence of immunohistochemistry (1980-2000) and those misclassifications might have biased some cancer clinical trial results. For this reason, old trial conclusions should be taken cautiously. Immunohistochemistry might be now overused with important implications for the debate on overdiagnosis/overtreatment and tumour classification simplification and harmonization could be a real step forward to minimize cancer overdiagnosis.[31] ISO 15189 standardisation should be seen as not a neutral endeavour, having important consequences for pathology diagnostic result accuracy, since most pathology diagnostic results are not quantitative but qualitative tasks.

In summary, further independent studies are required to emphasize and to determine more precisely the role of surgical pathology on overdiagnosis. Critical reading and understanding of pathology reports by general practitioners are essential. Therefore, family doctors should not hesitate to discuss the cancer diagnosis with the pathologist, and in some cases also question the oncologist decision. This approach can be considered a quaternary prevention action which can prevent overtreatment.

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