High Index of Clinical Suspicion With Optimal Surgical Techniques and Adjuvant Radiotherapy Is Critical to Reduce Locoregional Disease Progression in Parathyroid Carcinoma

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Aims: We have analyzed the risk factors and the impact of external beam radiotherapy (EBRT) in reducing the locoregional recurrence of parathyroid carcinoma (PTC).

Methods: Various parameters such as clinical presentation, intraoperative findings, surgical methods, and usage of parafibromin were analyzed. Selected endpoints were locoregional progression-free survival and overall survival.

Results: Three patients had local recurrence. Two of them received EBRT after the first recurrence but continued to have local recurrence. One patient was lost to follow-up. Six patients with EBRT remain asymptomatic with a locoregional progression-free survival and overall survival of 42 months. The presence of a palpable nodule in the neck, serum calcium >14 mg/dL, and intraoperative substrap adhesion (OR = 9.3, 95% confidence interval, 1.76-56.1; $P < 0.05$) should raise suspicion. Four of 5 patients showed a predominantly negative staining with parafibromin.

Conclusions: PTC should be suspected in the preoperative and intraoperative period. EBRT may reduce local recurrence by 65%. Parafibromin staining with no more than 0 to 1+ intensity in 80% to 100% of cells can predict carcinoma with specificity up to 100%.

Key Words: parathyroid carcinoma, risk factors, radiation, sub strap adhesion, local recurrence, palpable nodule

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BACKGROUND

Parathyroid carcinoma (PTC) is a rare disease, and its prevalence among patients with primary hyperparathyroidism is reported to be from 0.5% to 5%.[1] According to the available literature, the presence of experienced parathyroid surgeons in leading tertiary care institutions did not enhance the preoperative differentiation of PTC from adenoma beyond 15%.[2] Therefore, the higher rate of recurrence recorded could be due to suboptimal surgical procedures with or without piecemeal resection, resulting in tumor seeding the surgical field.

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The lack of preoperative and intraoperative suspicion and inadequate initial surgery could lead to locoregional recurrences of as high as 39%.[1] Tumor spillage is an independent risk factor associated with higher mortality. Radiotherapy has evolved as an important adjuvant therapy in a number of centers and has reduced local recurrence by 50% to 80%.[1] Optimal resection at the initial operation without tumor spillage is the key to avoid locoregional recurrence. Immunohistochemistry-based markers such as parafibromin are known to be poorly expressed in parathyroid cancer cells and are used as a marker in various studies.

AIMS

1. Could a high index of suspicion in the preoperative and intraoperative period help to minimize the recurrence rate?
2. Could the administration of external beam radiotherapy (EBRT) after the primary operation reduce disease progression or recurrence in PTC?

MATERIALS AND METHODS

The medical records of patients treated for PTC from 1988 to 2008 were analyzed. Age, clinical and biochemical features, intraoperative findings, surgical treatment, parafibromin staining, role of EBRT, and pathologic features were analyzed. We have also used our analyzed data on 248 patients with adenoma to compare various variables.

Immunohistochemical Staining Techniques

The expression of parafibromin, a 531-amino-acid protein product encoded by *HRPT2*, was evaluated using immunohistochemical techniques in 5 randomly selected paraffin blocks of PTC patients. The antibody used was mouse unconjugated antiparafibromin monoclonal antibody, clone 2H1, from Santa Cruz Biotechnology, Inc., at 1:350 dilution. Both the intensity and percentage of positivity were recorded and correlated with histopathologic features and clinical outcome. The adjacent normal parathyroid gland served as an internal control.

Selected endpoints in our study were locoregional progression-free survival (LRPFS) and overall survival (OS). LRPFS was defined as the length of time after surgery that the patient was free from clinical and/or pathologic tumor progression. Diagnosis was confirmed by the following pathologic criteria: (1) broad fibrous bands separating the tumor nests and the presence of capsular and/or vascular invasion; (2) invasion of contiguous neck structures (thyroid gland, trachea, strap muscles, esophagus, etc.); or (3) regional and/or distant metastases. Patients were required to have a minimum of 6 months

of follow-up. The role of EBRT and the importance of timing since primary surgery in reducing locoregional disease progression were analyzed.

Statistical Methods

Descriptive statistics (mean and standard deviation, frequencies) were obtained for all study variables. Association among categorical variables was assessed using the χ^2 test or the Fisher exact test, as appropriate. Odds ratios and 95% confidence intervals (CI) were also obtained.

RESULTS

During the study period, we had 10 (3.7%) patients with PTC among 245 patients with a confirmed diagnosis of primary hyperparathyroidism who underwent surgery. The mean age at presentation was 52 years (range, 20 to 87 y), and the male-to-female ratio was 2:1. We have compared the incidence of a palpable nodule in the neck of those patients with a diagnosis of adenoma and carcinoma. The incidence of a palpable nodule in benign adenoma was 20% as against 80% in carcinoma patients (OR = 9.3, 95% CI, 1.76-56.1).

Nine of 10 patients underwent a neck ultrasound preoperatively and did not have specific features to characterize malignancy, except 2 patients who had additional features such as cystic and hypoechoeic masses.

Of 10 patients, 6 underwent a Sestamibi scan (this imaging facility has been available at our center on a regular basis from 1998), and all 6 patients had features that were specific to hyperparathyroidism, except 1 who had additional central radiolucency of the mass.

The most common symptoms were renal stones (all patients: 10/10), nephrocalcinosis (2/10), bone pain, (10/10), fracture (2/10), chronic renal failure (3/10), and neuropsychiatric symptoms (2/10). Two patients presented with acute pancreatitis. The mean serum calcium level was 15.1 mg/dL (1.1), and intact parathormone (PTH) was more than 13 times that of normal with a mean of 1110.6 pg/mL (SD: 689.6). All of them except 2 (80%) had a hard palpable nodule in the anterior triangle of the neck at presentation.

The average size of the tumor was 2.3 cm (SD 0.2). For preoperative reduction of serum calcium, the patients received bisphosphonates, apart from adequate hydration.

Intraoperative findings were adhesions to the strap muscle, esophagus, and thyroid.

Table 1 depicts the extent of these adhesions. Adhesions between the tumor and strap (substrap adhesions) were seen in all the patients and represented either desmoplastic reactions or local infiltration. The incidence of substrap adhesions between benign and malignant disease was analyzed (Table 1). One patient with benign adenoma had minimal adhesion to the thyroid, which could represent local thyroiditis rather than adhesion from the parathyroid adenoma.

Of 10 patients, 7 received enbloc resection, and 6 patients received adjuvant EBRT; 1 patient died in the immediate postoperative period. This was an 87-year-old lady who presented with hypertensive crisis and malignant hypercalcemia. She underwent an emergency neck exploration. Despite adequate hydration and zolindronic acid administration, serum calcium was persistently high in the preoperative and intraoperative period. She succumbed in the immediate postoperative period because of cardiomyopathy-related complications.

The other 6 patients were disease free at 43 months of follow-up.

TABLE 1. Incidence of Substrap Adhesions and its Significance In Benign and Malignant Tumors

Local Vital Structures Involved	Benign (%)	Malignant (%)
Thyroid	1	20
Thyroid and strap muscles	0	60
Thyroid, straps, esophagus, trachea, and fascia	0	20
No adhesion	99	0
P		$P < 0.05$

Patients who had enbloc resection due to lack of preoperative and intraoperative suspicion underwent suboptimal en bloc surgical resection. Two patients developed locoregional recurrent disease at a mean follow-up period of 21 months after the primary surgery. The various surgical procedures and recurrence rates are depicted in Table 2.

Postoperative EBRT was given to 6 of 10 patients. The radiation dose to the neck was 50 Gy, spread over a period of 6 weeks. Three patients who did not receive EBRT in the immediate postoperative period developed local recurrence at 17 months. Two patients underwent reexcision of the neck mass because of local recurrence.

One of them underwent 4 surgeries for local recurrence, with a mean period of 39 months between procedures (Table 2). Both patients received EBRT after the locoregional recurrence. These patients presented with recurrence in the tumor bed and cervical nodal metastasis with elevated serum calcium at a mean follow-up period of 17 months after the administration of EBRT (Table 3). These 2 patients were followed up for a period of 112 months. One patient, who had pulmonary and skeletal metastases, succumbed after 16 years of diagnosis to chronic hepatitis C-related cirrhosis of the liver and urinary sepsis. The third patient with local recurrence was lost to follow-up. Six patients, who received EBRT in the immediate postoperative period, remain asymptomatic with LRPFS and OS of 42 months. The OS in the whole cohort was 43 months (SD 52.62.)

Parafibromin Staining

Four of 5 patients with PTCs showed predominant areas (80% to 100% cells) with negative parafibromin staining; 1 patient had focal faint (0 to 1+) staining in < 20% of cells.

DISCUSSION

PTC is rare, and in our series the incidence of PTC among primary hyperparathyroidism was 3.7%. This prevalence reflects only those patients with severe symptomatic hyperparathyroidism and may not reflect the true incidence of PTC. Most studies from Japan and developing countries report a significantly higher 5% incidence compared with most other studies from developed countries, which has been reported to be < 1%.[3,4] These differences could be due to a relatively underdiagnosis of parathyroid adenomas and a delayed presentation to the physician. The majority of patients with primary hyperparathyroidism in developing countries are diagnosed when they have asymptomatic hypercalcemia.[1]

Unlike parathyroid adenomas, in which the male-to-female ratio is 3:1, PTCs in most series have a 1:1[3] ratio. However, in our series, the male-to-female ratio was 2:1. Unlike parathyroid adenoma, which presents in the second and third decade, the PTC in our series was seen in the fourth and

TABLE 2. Surgical Treatment and Outcomes

	Intraoperative Findings		Treatment	Retreatment for Recurrence	Outcome
Primary en bloc resection (n = 7)	Substrap adhesions	7/7	Enbloc resection	Nil	6-Cured 1-mortality
	Peritumoral adhesion to prevertebral/paraesophageal area	5/7			
Primary inadequate resection (n = 3)	Substrap adhesions	3/3	Hemithyroidectomy and excision of the tumor	2 One patient × 4 Second patient × 1	1-lost to follow-up after recurrence 1-remission 1-mortality
	Peritumoral adhesion to prevertebral/paraesophageal area	3/3			

sixth decade. The mean age at presentation was 50 years (range, 20 to 87 y). The published adenoma series data from the developing world documented a female preponderance.[5]

The classic target organs of PTH, such as the kidney and skeleton, are affected with greater frequency and severity in PTC than in benign primary hyperparathyroidism. All of our patients had renal stones and bone disease: 2 patients also had chronic pancreatitis.

In adenomas, the mean serum calcium and PTH levels were much higher in patients from the developing world than in those from developed nations, which could be explained by their late presentation.

The published series from the developing world in adenomas stated a mean serum calcium level of 12.5 mg/dL (SD 1.6) and a mean PTH of < 10 times the normal.[4,5] However, the serum calcium and PTH levels of patients with PTC were much higher.[6] This was also seen in our series with a mean serum calcium level >15 mg/dL and intact PTH more than 14-fold higher than the upper limit. When we analyzed our unpublished data from the benign adenoma series, we found that the mean serum calcium level was 11.6 mg/dL, and PTH was 12-fold higher than normal. Odds ratios were calculated between these 2 groups. The risk of malignancy with serum calcium >14 mg/dL was significant (OR = 56, 95% CI, 5.1-105.1). However, serum PTH did not have such an association (OR = 4.3, 95% CI, 0.55-36.3).

A clinically palpable mass in primary hyperparathyroidism evolving from a benign adenoma in the western literature is 3%, whereas in the developing world it could be as high as 32%.[3–5] The discrepancy could be attributed to the delayed presentation, resulting in large adenomas in developing countries.[5] It was also interesting to compare the possibility of malignancy when the patient had a clinically palpable mass with primary hyperparathyroidism. The possibilities of malignancy in the presence of a palpable nodule was higher than when it was not palpable (OR = 9.3, 95% CI, 1.76-56.1). This important clinical finding is being described as being significant in the differentiation of benign from malignant parathyroid disease in other series as well.[7] According to Sandelin et al,[8] a patient with a clinically palpable nodule in the neck, without thyromegaly, and serum calcium >15 mg/dL, with severe systemic hypercalcemic symptoms, should raise the suspicion of PTC. In our series, 80% of the patients had a palpable nodule, and in other series it has been reported to be between 30% and 76%.[8]

Ultrasound in PTC has a limited role in preoperative diagnosis, and 9 patients in our series underwent a neck ultrasound scan. No specific characteristics were described in our patients, except 2 who had cystic, hypoechoic, and lobulated masses. These findings were also described by Huppart and colleagues. He also reported ultrasound findings differentiating adenoma from carcinoma. They are as follows: 1. a depth-to-width ratio >1 in 95% of carcinomas versus 5% in adenomas; 2. lobulated, inhomogenous, hypoechoic masses in carcinomas.[9]

Sestamibi scans are valuable in the preoperative localization of parathyroid lesions but do not distinguish between adenoma and carcinoma except when metastases are identified. No specific characteristic features could be identified in our series, except the image of 1 patient that showed a central radiolucency suggesting degeneration.

It is difficult to stage PTC, but Shaha et al[10] have described a staging system; while applying this classification to our study, all of our patients were observed to have stage 3 disease.

Preoperative fine-needle aspiration cytology is not advocated, as needle tract subcutaneous deposition could lead to local recurrences.[11–13] None of the patients in our series underwent preoperative fine-needle aspiration cytology.

As the tumor was palpable in 80% of cases, a gamma camera was not used preoperatively, and the investigator does not recommend a focused approach in cases in which there is a strong preoperative suspicion of carcinoma.

TABLE 3. Parathyroid Carcinoma Recurrence and role of EBRT

Outcome	Hemi Thyroidectomy Only (%)	Enbloc Resection (%)
Total	3 (33%)	7 (67%)
Recurrence with immediate postoperative EBRT	Not initiated	0
Postrecurrence EBRT	3 (100%)	N/A

EBRT indicates external beam radiotherapy.

Surgical Approach

In a large meta-analysis involving 266 patients, 26.9% of the patients underwent suboptimal surgical procedures, and only 13% underwent radical enbloc procedures.[14] Even in leading institutions with experienced parathyroid surgeons, up to 86% of cases of PTC were not suspected initially by the surgeon, resulting in inadequate surgical procedures.[14] Previous reviews have documented a higher rate of local recurrence (40% to 60% within 5 y) for PTC, with local implantation as the key source.[2,14,15] The conclusion that can be drawn from all these studies is the obvious fact that the first surgical procedure should be optimal and the tumor should be

excised with adequate soft tissue margin. In order to achieve this, the preoperative parameters of suspicion are critical.

In our series, carcinoma was suspected in 60% of patients in the intraoperative or preoperative period, and none of them had any recurrence ($P < 0.05$), whereas the recurrence rate was higher in 30% of the patients without preoperative or intraoperative suspicion, resulting in multiple surgeries (Table 4). The high local recurrence rate and failure to recognize or suspect preoperatively or intraoperatively have been well represented in other series[8,14,16] as the main cause of tumor recurrence.

We did not use the focused unilateral approach for neck exploration in these 10 patients; instead, a regular thyroidectomy incision was made. On the basis of our experience with the first 2 cases, if there was evidence of local desmoplastic reaction at the substrap level or if the nodule could not be reached because of local adhesions, the tumors were managed as carcinoma. Optimal surgical excision included ipsilateral hemithyroidectomy, central node clearance, and soft tissue resection, which included strap muscles and prevertebral fascia.[2,15,17] This constitutes an adequate primary enbloc resection.

The presence of substrap adhesions prompted us to manage 7 patients with enbloc resection, the terminology described to indicate an adequate surgical procedure. All 10 patients in our series had features of adhesions at the substrap level, which was significant to predict the malignancy ($P < 0.05$); apart from preoperative workup, high index of suspicion in the intraoperative period reduced the incidence of local recurrence to statistically significant levels, as depicted in Table 4 ($P < 0.05$).

When there was suspicion of carcinoma on the basis of preoperative and intraoperative findings, the investigator performed specific steps to avoid capsule breakage and obtain adequate soft tissue clearance. Table 4 shows that a high index of preoperative and intraoperative suspicion lowered the recurrence rate to a statistically significant level.

Steps of Enbloc Resection

After incising the skin and deep fascia, the strap muscles were retracted laterally; if substrap adhesions were encountered, the researcher considered it as a carcinoma and performed an enbloc resection.

Lower Pole Tumors

If there were substrap adhesions at the lower pole, strap muscles were resected at the level of the superior pole, followed by ligation of the superior thyroid vessels. The lower limit was reached by resecting the strap muscle beyond the tumor. Resection of the prevertebral fascia and the fibro-fatty tissue on the superolateral and inferior aspect of the thyroid lobe was performed. The lower limit of the lesion was approached by gentle sharp/peanut dissection beyond the limit of the tumor.

Lateral adhesions along with perioesophageal tissues were then resected. In view of extensive fibrosis, 2 patients had nasogastric tubes placed intraoperatively to identify the esophagus. The mass and thyroid lobe were then flipped medially, and hemithyroidectomy along with ipsilateral central node clearance was performed. Nodal clearance and ligation of the lower pole vessels were carried out at the end of the procedure to avoid untoward traction or pull in the capsule, which might result in tumor spillage, which is an independent factor in local recurrence.[18] The recurrent laryngeal nerve was identified and preserved in all patients.

In upper pole tumors, the lower pole was dissected first after resecting the strap muscles at the lower pole level; the recurrent laryngeal nerve was identified and preserved. The rest of the dissection was the same as that of the lower pole tumors, and the superior pole was ligated at the end. Care was taken not to breach the pharyngeal wall. We have operated on 1 patient with postradiation tumor recurrence, and the usage of a nasogastric tube was very helpful in the identification of the esophagus.

Lateral neck nodes are unusual, and the percentage of positive nodes could be from 8% to 17%, as shown in a large meta-analysis; dissection is indicated only when there is evidence of spread to the anterior cervical nodes.[2,14,15] In these series, nodal disease was seen to be more with local recurrences, and this finding was also observed in our series. Two patients had nodal disease after local recurrence. In other studies, metachronous lymph node metastases occurred after local recurrence was included with primary cases, thus inflating the lymph node positivity rates to as high as 32%.[8,16] In our series as well, there were no lymph nodal or distal metastases until the development of local recurrence. We do not recommend a prophylactic neck node dissection.

Surgical Pathology

The absolute criteria for malignancy include the presence of invasion into adjacent structures or the presence of metastasis. In the absence of the above features, the presence of ≥ 2 atypical microscopic features such as capsular invasion, vascular invasion, mitotic activity of >5 per 10 hpf, broad intratumoral bands, coagulative tumor necrosis, diffuse sheet-like arrangement of cells with high nucleocytoplasmic ratio, and macronucleoli in most of the tumor cells favors a diagnosis of malignancy.[19] All our patients had capsular invasion

TABLE 4. Index of Suspicion in the Preoperative and Intraoperative Period and the Incidence of Malignancy and Recurrences

Index of Suspicion	N (%)	Malignancy	Recurrence (%)
Yes	70	7	Nil
No	30	3	3

Index of suspicion of substrap adhesion or local fibrotic reaction, along with palpable nodule and serum calcium >14 mg ($P < 0.05$).

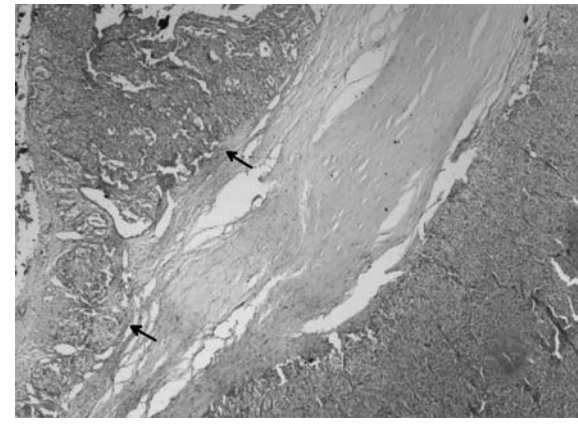

FIGURE 1. The capsular invasion. The arrows indicate the area of invasion.

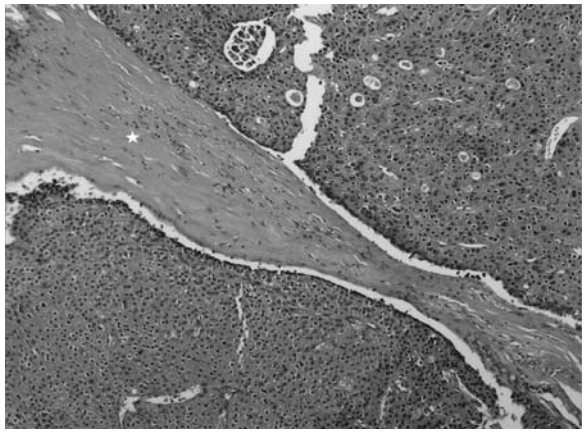

FIGURE 2. The broad intratumoral fibrous bands. The asterisk indicates the broad bands.

and additional histologic features such as vascular invasion and broad intratumoral fibrous bands, which are depicted in Figures 1 and 2.

Immunohistochemistry Staining

Parafibromin immunostaining was carried out at a dilution of 1:350. We had performed parafibromin nuclear staining on 5 cases, of which 4 had 80% to 100% of cells with 0 to 1+staining and 1 patient had 30% cells with positive staining, resulting in a sensitivity of 80% and specificity of 100%. In other series, sensitivity was reported to be 85% to 99% and specificity was 92% to 100%;[19] however, in those PTCs arising in HP-JT syndrome or with microcystic change on histology, the parafibromin can be negatively stained.[20]

Role of External Radiotherapy

EBRT is becoming an important adjuvant therapy. From the Mayo series and other data, it is evident that the local recurrence rate without EBRT is 77%,[1,21–24] whereas in patients who had EBRT the recurrence rate is only 17%. In our series, the adjuvant EBRT seems to have reduced recurrence by 65%, and the recurrence rate among patients who did not receive immediate EBRT was 100%. Of 3 patients with local recurrence after primary surgery, 1 patient was lost to follow-up after the second operation for recurrence and did not receive EBRT. Two patients received EBRT after local recurrence. In these patients, there was locoregional disease progression, and 1 patient developed distant metastasis to the lung and bone at 180 months of follow-up. Therefore, it is evident that administration of radiotherapy soon after the initial surgery could be beneficial in reducing locoregional recurrence. The 3 recurrences that we observed occurred within the first 2 years and then disease recurred in them at regular intervals. Therefore, it is mandatory that these patients be followed up for a long term.

In another large series, 26 of 43 patients (60%) who did not receive EBRT required a second operation, with 18 of them requiring multiple reexplorations.[21] We had 3 of 10 patients who needed subsequent surgical procedures (33%). The low recurrence in our study could have been partially attributed to a more complete resection because of a high index of suspicion in the intraoperative period. We had 1 patient who developed radiation-induced hypothyroidism (16%).

Although radiation exposure enhances the risk of hypothyroidism and the need for long-term follow-up of the other lobe of the thyroid, this need not deter one from using it in PTC.

Prognostic Factors

With the available data, we did not observe any significant association between recurrence and factors such as sex, age at diagnosis, tumor size, or preoperative calcium level. The single most important factor in the prediction of malignancy was substrap adhesions, (Table 3) which were directly related to the surgical decision and outcome. The importance of enbloc dissection has been emphasized in this paper, which was a very significant step in the prevention of recurrence. The timing of EBRT also seemed to be crucial as 2 patients continued to have local recurrence despite EBRT, which was administered after the first recurrence.

Six patients who received EBRT in the immediate postoperative period remain asymptomatic with an LRPFS and OS of 42 months. The mean LRPFS among patients who did not receive EBRT was 17 months. The OS in the whole cohort was 43 months (SD of 52.62).

The 5-year and 10-year overall disease-specific survival rate was 100%, as the 2 deaths were unrelated to PTC.

Limitation of the Study

Given the fact that PTC is a rare disorder, forming guidelines to manage this disease is extremely difficult. Despite our small numbers, we have made an attempt to address the steps to reduce the recurrence rate of this disease.

CONCLUSIONS

PTC should be clinically suspected if a patient has a serum calcium level >14 mg/dL with a palpable nodule in the neck and intraoperative findings such as substrap adhesion or local fibrotic reaction. It is prudent to manage these preoperatively or intraoperatively suspected cases as carcinoma with enbloc resection of the tumor to reduce the locoregional recurrence rate. Usage of EBRT in the immediate postoperative period may reduce the local recurrence rate by 65%. Parafibromin staining with no more than 0 to 1+ intensity in 80% to 100% cells could predict carcinoma with specificity up to 100%.

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