ANTICANCER RESEARCH *24*: 1179-1186 (2004)

Detectable Serum PSA After Radical Prostatectomy. Clinical and Pathological Relevance of Perianastomotic Biopsies

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Abstract. *Background: Few reports have detailed the histopathological results of biopsies of the vesicourethral anastomosis or prostatic bed in patients with a detectable postoperative PSA. Patients and Methods: Among a series of 153 patients who underwent radical retropubic prostatectomies, we analyzed the results of 64 perianastomotic biopsies performed in 17 men with a detectable PSA and no evidence of local recurrence or distant metastases. Results: Fourteen of the 17 patients had a relapse of prostatic carcinoma; the results of histology in the three $pT_{2b}N_0M_0$ patients revealed the presence of benign prostatic hyperplasia in 2 patients and atypical cribriform proliferation in 1 patient. The first two patients are free from prostatic cancer recurrence 36 months after perianastomotic biopsies; a further biopsy performed 6 months after in the third patient showed the presence of prostatic carcinoma. Conclusion: The present study raises the possibility that residual benign tissue, resulting from unintentional disruption of the prostatic capsule during surgery, may be responsible for a detectable postoperative PSA. These cases comprise a histopathological classification described as "intraprostatic surgical margin".*

Serial PSA measurements after radical prostatectomy for locally confined prostate cancer have become the most widely used means to monitor disease recurrence since the introduction of PSA into clinical routine practice in the late 1980s (1). Thus increase in PSA level represents the earliest and most reliable method for diagnosing recurrent disease (2). Although PSA is prostate-specific and not cancer-specific, any rise in PSA level after radical prostatectomy will probably be caused by cancer progression and only in rare cases by residual benign disease (3). Many studies have observed that cancer at the inked surgical resection margin of the radical prostatectomy specimen may suggest that local resection has been incomplete (4-11). Fewer reports have detailed the results of biopsies of the vesicourethral anastomosis or prostatic bed in patients with a detectable postoperative PSA.

In the present study we analysed the results of 64 anastomotic biopsies performed in 17 men with a detectable PSA after radical prostatectomy, aiming to observe the causes of biochemical failure after radical prostatectomy.

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Key Words: Prostate specific antigen, radical prostatectomy, biochemical failure, perianastomotic biopsies, intraprostatic surgical margin.

Patients and Methods

From the database of 230 radical prostatectomies performed at our Institute from 1989 to 1999 with an up-to-date follow-up, we considered 153 men (mean age 65.7 years, range 46-75), who underwent pelvic lymphadenectomy and radical retropubic prostatectomy for prostate cancer between 1992 and 1999.

Pre-operatively all the patients, according to a protocol developed in cooperation with the Institute of Pathology of the University of Ancona, Italy (12), underwent a 3-month course of neoadjuvant androgen deprivation therapy (13-17). Eighty-eight patients were $pT_2N_0M_0$ and 65 patients were $pT_3N_0M_0$; the Gleason score was 2-4 in 46 patients, 5-7 in 69 patients and 8-10 in 38 patients.

The prostatectomy specimens were delivered fresh from the operating room shortly after excision and stained as described (18).

Clinical follow-up had been recommended to all patients according to our protocol, even if not all the patients agreed to adhere to it. The patients were followed-up for a mean period of 57.7 months (range 24-116 months); they were generally seen by a urologist at 3-month intervals; a digital rectal examination and a PSA measurement were performed at each visit by the Central Laboratory of the Hospital, estimating the PSA level with a sensitivity threshold of 0.001 ng/ml.

Time to PSA progression, PSA doubling-time and PSA velocity were considered as well, and a correlation was made to assess whether these analyses could predict the type of recurrence. Patients, with a detectable PSA (biochemical failure was defined as having 2 or more consecutive levels of 0.4 ng/ml or greater as reported in the literature) (19) and no evidence of local recurrence or distant metastases on physical examination,

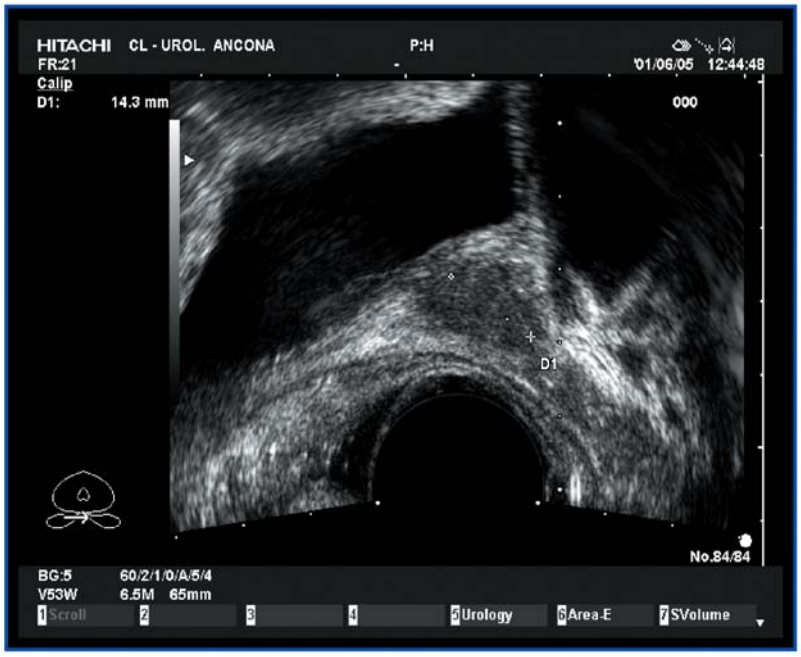

Figure 1. *Ultrasound appearance in a patient with local recurrence using end-fire 7.5 probe.*

Figure 2. *Image of local recurrence using echo-color power doppler, with evidence of hypervascularity in the hypoechoic tissue around the anastomosis.*

Table I. *Correlation between baseline PSA and surgical margins in patients after radical prostatectomy.*

Baseline PSA ng/ml	No. of patients	Surgical margins (negative)
< 4	12	12 (100%)
4.1-10	37	29 (78%)
10.1-20	44	29 (66%)
20.1-35	25	10 (40%)
> 35	30	12 (40%)

chest X-rays or radionuclide bone scan, underwent transrectal ultrasound and ultrasound-guided biopsies of the vesicourethral anastomosis.

In preparation for the procedure, the patients were generally treated with thrimethoprim-sulfametoxazole for 1 day before and 2 days after the biopsy and received a Fleet enema 2 hours before the biopsy. Using a 18-gauge needle (Bard Max-Core) and an end-fire ultrasound probe (Hitaci-Esaote), 1 or 2 specimens for each side of the vesicourethral anastomosis were taken under ultrasound guidance and, if present, 1 or 2 biopsies were taken from a visible abnormal lesion.

Table II. *Characteristics of radical prostatectomy patients.*

No. of pts	Mean age	Pathological stage	Surgical margins	Gleason score (LH-RH)	Adjuvant therapy	Mean time to PSA increase	Mean PSA ng/ml	Histology of anastomotic biopsies	Therapy of local recurrence
2	62.5	PT_{2b}	M +	3 + 3	6 months	42 months (24-60)	2.5 (3-2)	Prostatic carcinoma	Hormones
1	62	pT_{3a}	M +	3 + 3	12 months	40 months	3	Prostatic carcinoma	RDT
8	65.3 (51-72)	pT3b	M +	3 + 3 (4) 3 + 4 (4)	12 months	36.5 months (15-110)	2.72 (1-5)	Prostatic carcinoma	Hormones 5 RDT 3
2	64	pT_{2b}	M 0	3 + 3	No	22 months	2 (20-24)	Benign prostatic hyperplasia	None
1	67	pT_{2b}	M 0	3 + 3	No	108 months	1.5	Atypical cribriform proliferation	Peripheral androgenic blockade
1	61	pT_{3a}	M 0	3 + 3	12 months	36	2	Prostatic carcinoma	Hormones
2	66 (64-66)	pT_{3b}	M 0	3 + 3	12 months	27 (24-30)	1.5 (1-2)	Prostatic carcinoma	Hormones

M0 = negative surgical margins; M+ = positive surgical margins; RDT = radiotherapy

Results

At pathological examination of the surgical specimen, 12 out of 12 patients (100%) with baseline PSA < 4 ng/ml had negative surgical margins, 29 out of 37 patients (78%) with baseline PSA between 4.1-10 ng/ml had negative surgical margins, 29 out of 44 (66%) patients with baseline PSA between 10.1-20 ng/ml, 10 out of 25 (40%) patients with baseline PSA between 20.1-35 ng/ml and 12 out of 30 (40%) patients with baseline PSA higher than 35 ng/ml had negative surgical margins (Table I).

Of the 153 study patients, a detectable PSA was noted in 56 (36.6%) cases after surgery; of them 39 patients had pelvic recurrence (diagnosed by radiographic imaging) (16 patients), visceral (3 patients) or bone (20 patients) metastases, while 17 patients had no evidence of pelvic recurrence or distant metastases and therefore underwent transrectal ultrasound and biopsies of the vesicourethral anastomosis (Figures 1 and 2). There were no episodes of fever, chills or significant bleeding after the biopsies, although self-limiting gross hematuria was not uncommon. A total of 64 (min 2–max 5, mean 4) biopsies were performed on the 17 patients. In Table II the characteristics of the patients who underwent anastomotic biopsies can be observed; the mean age of these patients was 63.3 years; 5 patients showed a T_2 and 12 patients showed a T_3 pathological staging.

Patients with a specimen-confined disease (pT_{2-3}) and negative surgical margins (71.3%, 164/230) did not undergo hormonal adjuvant treatment; patients with positive resection margins (pT_{2-3}) (29.7%, 66/230) underwent a 6-month hormonal adjuvant treatment; but patients with seminal vescicles invasion (pT3b) (9.5%, 22/230) or metastatic lymph nodes (pN1) (12.6%, 29/230) underwent a 12-month course of hormonal adjuvant treatment (12).

The mean time to biochemical failure was 50.6 months (range 20-108) for T_2 tumours with negative margins of resection, 42 months (24 and 60 months) for T_2 tumours with positive margins, 30 months (range 24-36) for T_3 tumours with negative margins and 36.8 (range 15-110) for T_3 tumours with positive margins. At the time of biochemical failure, the mean serum PSA was 1.75 ng/ml in T_2 tumour with negative margins, 2.5 ng/ml for T_2 tumour with positive margins, 1.66 ng/ml (range 1.0-2.0) for T_3 tumours with negative margins and 2.98 (range 1.0-5.0) for T_3 tumours with positive margins.

All the 17 patients except for 3 had a local relapse of prostatic carcinoma; the results of histology in the 3 $pT_{2b}N_0M_0$ patients revealed the presence of benign prostatic hyperplasia in 2 cases and atypical cribriform proliferation in 1 case (Table III).

The PSA velocity was 0.50 ng/mL/year in patients with cancer, while it was 0.15 ng/mL/year in patients with benign tissue (Figure 3); PSA doubling-time was 9.1 months for patients with cancer on biopsy, while it was 15.3 months in patients with benign tissue on perianastomotic biopsy (Figure 4).

The two patients whose biopsies revealed benign tissue are free from prostatic cancer recurrence 36 months after perianastomotic biopsies; a further biopsy performed 6 months

Table III. *Characteristics of primary prostate cancer in patients with local recurrence.*

Data	Local recurrence	Benign prostatic tissue	Atypical gland & benign tissue
No. of patients	14	2	1
Mean follow-up (range)	57.7 (24-116)	56 (46-72)	108
Mean follow-up to PSA failure	39 (15-110)	30	36
pT_{2b} surg marg (-)	0	2/2	1/1
$pT_{3a/b}$ surg marg (-)	3/14 (21%)	0	0
pT_{2-3} surg marg (+)	11/14 (70%)	0/2	0/1
Gleason score ≥ 7	4/14 (30%)	0/2	0/1
Perineural invasion	9/14 (65%)	0	Not available
Vascular invasion	4/14 (30%)	0	Not available
Seminal vesicles invasion	10/14(70%)	0	0
Tumor volume < 0.6 cc	0/14	2/2 (100)	1/1
PSA velocity (ng/ml/year)	0.50	0.15	0.20
PSA doubling time (months)	9.1	15.3	14.9
PSA at biopsy (mean)	2.7	2	1.5
US features	Hypoechoic area	Small isoechoic area	Small isoechoic area
Suspicious DRE	6/14	0	0
Neoadjuvant hormonal therapy (3 months)	14/14	2/2	1/1
Adjuvant hormonal therapy	Yes	No	No

after in the third patient showed the presence of prostatic carcinoma and the patient underwent hormonal therapy.

All the patients with biopsies revealing the presence of prostatic carcinoma underwent additional treatment: hormonal treatment in 10 cases and radiotherapy (RDT) in 4 cases. Possible side-effects, *e.g.* proctitis and adverse effects on continence, are of concern for the patients when deciding on radiotherapy (even if recommended) *versus* hormonal treatment.

Discussion

After radical prostatectomy, the serum PSA should fall to undetectable levels; as progression is almost invariably accompanied by a rising PSA level, patient monitoring by periodic serum PSA determination should be performed (20). Normally, biochemical failure precedes clinical disease by 6-48 months (21); elevations occurring less than 2 years postoperatively, and in particular PSA doubling occurring less than 2 years postoperatively, have been associated with distant disease (22). Among the patients who develop biochemical recurrence following radical prostatectomy, up to 50% may have local disease alone, while the remainder have distant recurrence or local plus distant recurrence (23).

This study represents the result of our experience in the treatment of patients with clinically organ-confined prostate cancer; the patients included in this study do not represent a screening-based population, this possibly accounting for the high percentage of pT3 patients and for the high PSA recurrence rate after radical prostatectomy [36.6% in comparison to lower rates observed in other studies (24 - 26)].

These patients underwent pre-operative androgen ablation to reduce tumour and gland volume, since most of them had clinically cT_{2b} tumour, PSA >10 ng/ml and tumour Gleason score ≥7 in 80% of cases. Androgen ablation could reduce detection of cancer in surgical margins, but in all cases tumour foci were easily identified by the pathologist on the basis of different degrees of hormonal-induced changes or immunohistochemistry for PSA. However, a short-term (3 months) androgen ablation did not significantly influence PSA rising after radical prostatectomy in patients with restored levels of serum testosterone (12, 27).

Patients with $pT3_{b/c}$ tumour and/or with positive surgical margins, who were considered at high risk of recurrence, underwent a long term additional hormonal suppressive therapy. Tumour recurrence was identified after a long time, delaying the PSA rise by 2 years, since restoring the testosterone production was a long process.

This study confirms, once again, that a recurrent tumour after radical prostatectomy is preceded by an increase of serum PSA (*i.e.* biochemical failure), but a detectable PSA does not necessarily mean the manifestation of recurrent cancer. It has been observed that, after radical prostatectomy, 27-53% of men can show a PSA increase (2, 24, 28-30).

Many studies have shown that neo-adjuvant hormonal therapy before radical prostatectomy has a strong influence on some important parameters (31). To our knowledge, the influence of neo-adjuvant therapy on the histology of perianastomotic biopsies has not yet been investigated; on the basis of what has been already observed (12, 31), this could be the reason for a decreased incidence of prostatic carcinoma in perianastomotic biopsies after preoperative androgen deprivation; in fact, the incidence of prostatic carcinoma at the level of perianastomotic biopsies in our series was high (15 out of 17 patients).

In assessing local recurrence, the digital rectal examination is of limited value because of the difficulty of differentiating benign scar tissue from recurrent prostate cancer (32). However, biopsy and subsequent histology can be an unreliable means of confirming local recurrence, because only half the patients are diagnosed correctly on the first biopsy and about 30% need two or more biopsies of the vesicourethral anastomosis to identify recurrent cancer (2, 33).

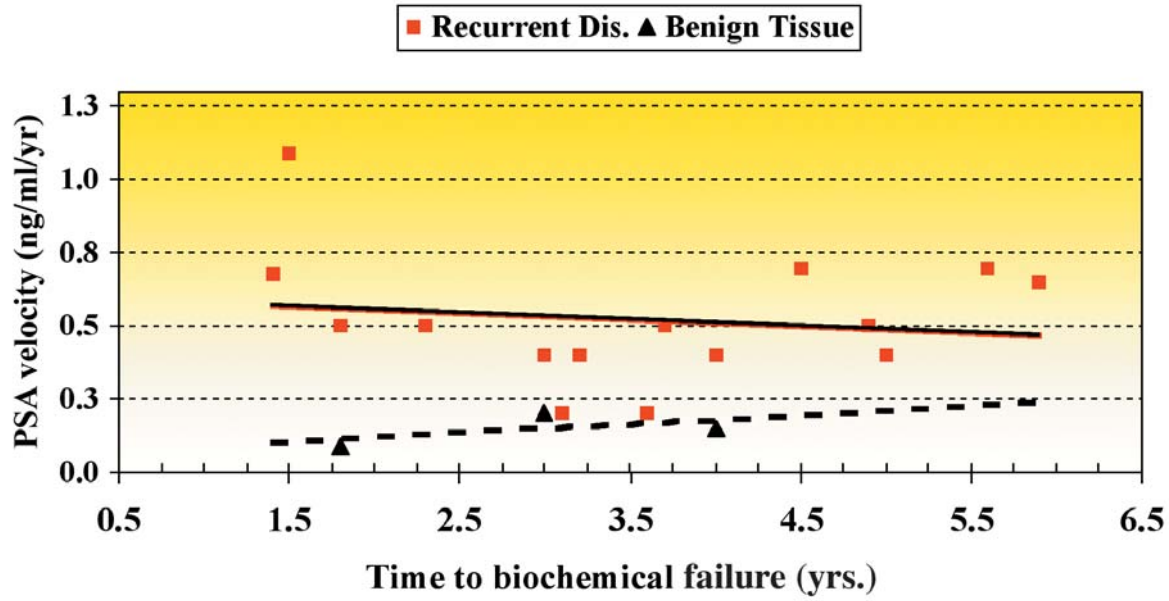

Figure 3. *Histology of anastomotic tissue biopsy and PSA velocity.*

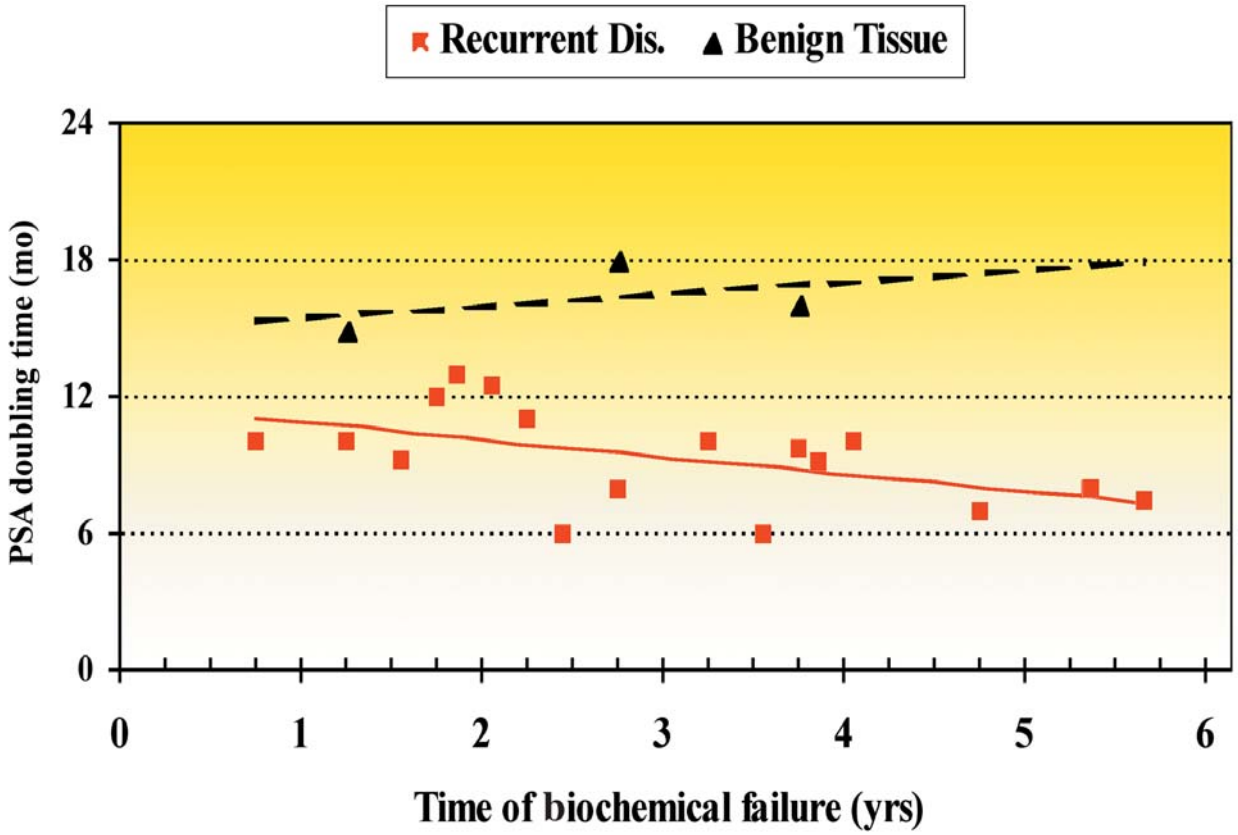

Figure 4. *Histology of anastomotic tissue biopsy and PSA doubling time.*

Our study, as observed by others (34), raises the possibility that residual benign tissue resulting from unintentional disruption of the prostatic capsule during surgery (*i.e.* incomplete resection of the apex) may be responsible for a detectable postoperative PSA.

There is no agreement about the significance of fibromuscular tissue in patients with a detectable PSA after radical prostatectomy, since it has been observed that 30% of patients with documented residual cancer had one or more earlier biopsies that revealed fibromuscular tissue only (3); others have reported that 58 to 65% of patients with a detectable PSA after radical prostatectomy will have an unrevealing initial biopsy (35, 36) and that 47% of such patients will have carcinoma documented with subsequent biopsies (25).

Koppie *et al.* observed that detecting recurrent prostatic cancer by transrectal ultrasound-guided biopsies is less common in patients with low post-prostatectomy serum PSA, which is probably due to low volume disease (37). A positive biopsy was noted in 50% of patients with serum PSA 0.5 to 1 ng/ml and in 28% of patients with PSA less than 0.5 ng/ml. Local recurrence was noted at the anastomosis in 66% of patients. The authors conclude that anastomotic biopsy is not necessary for confirmation of recurrence and a raised PSA level alone is adequate for decisions regarding local radiation therapy after radical prostatectomy.

Shah *et al.* (38) observed that excising and submitting an additional 2 to 3 mm of apical soft tissue margin for permanent section analysis after prostate removal during radical prostatectomy represents an effective method for decreasing residual prostate tissue. Tongco *et al.* (39) observed that residual adenoma after radical retropubic prostatectomy may confound follow-up results.

The cases in our series were infrequent, but it may happen that biochemical failure is not related to tumour recurrence, since an incomplete resection of the prostatic apex may leave residual prostatic tissue. These cases comprise a histopathological classification described as "intraprostatic surgical margin". The criteria to define a positive surgical margin at the apex include the presence of a tumour that reaches the margin of section and it is called pT_{2c} according to the 1997 TNM classification. Because of the lack of the fibrous capsule at the apex of the prostate it is difficult to say if the urethral stump, that remains *in situ*, is surrounded by benign prostatic tissue; therefore it is easy to define a surgical margin free from cancer, but it is difficult for the pathologist to identify the complete removal of the prostate at the level of the apex.

The inconvenience of finding normal prostatic tissue in anastomotic biospies can be avoided by the macroscopic and microscopic analysis of the urethral stump and of the whole fresh prostatic gland as soon as delivered from the operating theatre; this can allow a careful identification of the distal urethra. The presence of glandular tissue surrounding the urethra indicates the presence of a intraprostatic surgical margin and an incomplete resection.

The clinical significance of prostatic residual tissue in follow-up is most important since it can be responsible for biochemical failure and can increase in size, simulating in this way a local recurrence. The anastomotic biopsy is indicated in patients with clinical suspicion of local recurrence, that of course cannot be diagnosed only by serum PSA, digital rectal examination or imaging techniques.

Low but significant PSA levels after radical prostatectomy can be associated with intraprostatic surgical margins. The accurate analysis of the biopsy should describe the presence of normal prostatic tissue or of neoplastic tissue, since these findings are of great importance from the clinical point of view.

Therefore, in the presence of biochemical failure after radical prostatectomy, we need to perform anastomotic biopsies and review the histological surgical specimens.

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Received November 7, 2003
Revised January 29, 2004
Accepted February 24, 2004