Functional and ongological results of radical perineal prostatectomy for the management of clinically locally advanced prostate cancer. Single centre experience

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Summary
Introduction
Radical prostatectomy is considered to be the best choice for managing localized prostate cancer. There is increased evidence that a surgical approach has an important role to play as a method of treatment for locally advanced prostate cancer. According to the European Association of Urology (EAU), radical prostatectomy is an option for properly chosen patients with locally advanced prostate cancer. The aim of our study is to evaluate the oncological and functional results of radical perineal prostatectomy for the management of patients with clinically locally advanced prostate cancer.

Methods
Between 1993 and 2012, 627 patients underwent radical perineal prostatectomy for histologically confirmed prostate cancer. Eighty three out of 627 patients had clinically advanced disease. Perioperative morbidity, functional results and early oncological outcomes were examined and compared between the two groups.

Results
There was no statistically significant difference between the two groups regarding operation time, intraoperative blood loss, length of hospital stay and duration of catheterization. The rate of complications was also similar, with the exception of two rectal injuries in the locally advanced group, though these were successfully repaired at the same time. In the locally advanced group, 17.3% of the clinically advanced patients had pathologically confined disease. Out of the patients 99.8% remained continent and 36.1% remained potent in the locally advanced group. In the organ confined group the rates were 100% and 62.5%, respectively. Between the two groups there was no significant difference regarding the cancer-specific survival rate.

Conclusion
Radical perineal prostatectomy is considered to be the best choice for treating locally advanced disease, provided patients are fully informed and that they consent to undergo this treatment.

Key Words
Radical perineal prostatectomy, locally advanced prostate cancer.

Introduction
Treatment of clinically locally advanced prostate cancer is considered to be a medical challenge for a urologist. Even today, selecting an appropriate treatment is a subject of research. Surveys show that a greater overall benefit results from combined treatment (radiotherapy together with hormone therapy) instead of monotherapy (using only radiotherapy). However, no study has ever proved that combined treatment is a better choice than radical prostatectomy.
In the past, surgical treatment of locally advanced prostate cancer was not often resorted to due to an increased risk of positive surgical margins, and also due to existence of lymph node metastases. Nowadays there is an increasing number of reports in the literature that support radical prostatectomy as a legitimate solution to manage locally advanced disease. This has led the European Association of Urology (EAU) to consider radical prostatectomy as a potential option to a selective range of patients with locally advanced disease. (cT3).

The literature refers to retropubic radical prostatectomy and perhaps for the first time in this study we attempt to promote the significant role of perineal access to deal with pre-operatively diagnosed, locally advanced prostate cancer. In our clinic (Department of Urology 401 G.M.H.A) since 1993, radical perineal prostatectomy has been not only the method of choice, but the only surgical method of access to prostate cancer. In our given material we do not have any other method, and for that reason in this study we attempt to compare our results to other authors, as these are found in the international literature.

Material and methods
This study refers to 627 radical perineal prostatectomies that were conducted in the Department of Urology in the 401 Military Hospital of Athens, between 1993 and 2012. Diagnosis of this disease was conducted with a transrectal ultrasonographically guided prostate biopsy. Typically, 5 or 6 tissue blocks were extracted from each lobe and also from suspicious areas detected in a digital examination or in the transrectal ultrasound, regarding either intraprostatic fat, or the seminal vesicles. Clinical staging was accomplished through digital examination, transrectal ultrasound and CT scan, and showed 83 patients with locally advanced disease. There was no patient selection in reference to prostate size or somatometric measurements, while 35 of the patients had already been submitted to pre-operative hormonal manipulation to achieve shrinking of the tumor. Properties of each group are shown in Table 1.

**Table 1** Characteristics of the patients treated with radical perineal prostatectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Average age (years)</td>
<td>62.7 (51-73)</td>
</tr>
<tr>
<td>Gleason score biopsy</td>
<td>7 (4-9)</td>
</tr>
<tr>
<td>PSA</td>
<td>13.38 (5.5-42)</td>
</tr>
<tr>
<td>Laparoscopic Lymphadenectomy</td>
<td>77.1%</td>
</tr>
<tr>
<td>Unilateral preservation of Neurovascular bundle (INVB)</td>
<td>43.3%</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>37 (8-62)</td>
</tr>
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laparoscopic lymphadenectomy, which has been practiced since 1994, was based on the preoperative PSA value and the biopsy Gleason score. Patients with PSA lower than 10 and a Gleason score <719 (19 patients) were excluded. For the statistical analysis, we used Pearson chi-squared test for independence. Due to the zero-frequency of some parameters (no appearance), the calculation of p-value (observed statistic level of importance) for this test was not asymptotic (that is, with the use of the chi-squared distribution), but was calculated with the use of a Monte-Carlo simulator. The result was considered to be statistically significant when p-value was less than 0.05 (the level of statistical significance).

Results
Average duration of the operation was 175 min, including the average 60 min duration time of laparoscopic lymphadenectomy for the locally advanced group. Average blood loss was 280 ml. In comparison to the 544 patients with localized disease, the difference was statistically insignificant (p-value=0.150)(168 min and 250 ml, respectively). There was also an insignificant difference in postoperative complications as well, with the exception of two intraoperative rectal injuries in the group of locally advanced disease, which were successfully repaired. Also in one patient from the locally advanced group, the formation of a urinary fistula was observed. The removal of the penrose drain was difficult, possibly being caught on the stitches of the pelvic musculature.

After penrose drain removal, on the 1st postoperative day, an outflow of urine was observed through the wound that continued for 2 weeks, when a small penrose drain remnant was spontaneously retracted. The urinary incontinence was successfully resolved via additional catheterization for the following 2 weeks, without any further intervention (table 2).

Erectile Function was tested 12 months postoperatively. 36.1% of the patients reported erection capable of vaginal penetration in the group of locally advanced disease (30 patients), significantly lower than the respective rate of localized disease.

Table 2 Complications after radical perineal prostatectomy

<table>
<thead>
<tr>
<th>complications</th>
<th>LOCAL DISEASE</th>
<th>LOCALLY advanced disease</th>
<th>ADVANCED</th>
</tr>
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<tbody>
<tr>
<td>Death rate</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bowel Injury</td>
<td>0</td>
<td>2 (.4%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lymphocele</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anastomatic stricture</td>
<td>11 (.2%)</td>
<td>2 (.4%)</td>
<td></td>
</tr>
<tr>
<td>Compartment Syndrome</td>
<td>1 (.16%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Urinary Fistula</td>
<td>0</td>
<td>1 (.12%)</td>
<td></td>
</tr>
</tbody>
</table>

(62.5%) (P-value<0.05). This is due to the unilateral preservation of neurovascular bundle only in 43.3% of the patients with clinically locally advanced disease, due to local extention of the disease. In a single patient with invasion of the prostate apex, incontinence persisted 12 months postoperatively which was resolved with implantation of an artificial urinary sphincter. As for the oncological results, pathologic down staging was observed in 16.8% of the patients with clinically diagnosed, locally advanced disease (p-value<0.05) (Table 3).

Table 3: Pathological stage distribution after radical perineal prostatectomy

| pT1a | 16.8% |
| pT1b | 48.2% |
| pT1c | 31.4% |
| pT2 | 3.6% |

Positive surgical margins were found in 14.4% of the group with clinically advanced disease in comparison to 12.5% of the group with the localized disease. Positive lymph nodes were detected in 10 out of 83 patients with clinically locally advanced disease (12%). The preoperative CT scan evaluation showed no sign of lymphnode metastasis. In the first case patients underwent adjuvant
radiotherapy while in the second case they underwent hormonal deprivation. During the follow-up period, 28.1% of the patients received adjuvant or salvage radiotherapy due to positive surgical margins or biochemical relapse, indicative of local relapse, and 33.7% received hormonal therapy due to lymphatic metastasis or biochemical relapse indicative of systemic disease. The disease specific survival in the first three years was 93.9% in the group of clinically locally advanced disease and 96% in the group of localized disease.

**Discussion**

Selection of the therapeutic treatment of clinically advanced cancer is a challenge for the urologist. The goals of treatment should include: healing; extension of life, although this should be achieved without any metastasis; localized control of the tumor; and improvement of quality of life. The therapeutic choices for the achievement of the above are various. Prognosis varies widely, and the choice of treatment depends on predictive factors such as PSA value, Gleason score and tumor size. According to the EAU guidelines, watchful waiting may be conducted even inpatients without symptoms, with well- or moderately-differentiated T3 disease, and life expectancy of less than 10 years, who are not able to undergo surgery or radiation treatment. Radical prostatectomy is considered an option in a selective range of patients with T3a, PSA<20ng/ml, biopsy Gleason score <8 and life expectancy lower than 10 years. According to the EAU, those patients should be aware that radical prostatectomy is related to increased risk of positive surgical margins and lymph-node metastasis, which need adjuvant radiotherapy or hormonal therapy, respectively. Amongst the patients with clinically diagnosed, locally advanced disease in the study, 16.8% were eventually diagnosed with pT2 disease and as a result it was not necessary to follow adjuvant treatment. If we take into consideration the low rate of intraoperative complications and the satisfactory functional results, these patients benefited from undergoing an operation of lower severity such as perineal prostatectomy, which in our experience allows for the preservation of critical structures, just as much in the case of locally advanced disease, as in that of localized. During the follow-up the percentage of patients who received treatment was 28.1% and 33.7% for local radiotherapy and hormonal therapy respectively.

In the literature there are not series of patients with clinical locally, advanced cases of the disease who underwent radical perineal prostatectomy, and therefore comparisons can be made only with series which have undergone retropubic prostatectomy. The reported results in those cases arise from strictly selected cases; such selection did not occur in our study for the reasons explained above.

Downstaging in clinical locally advanced disease in pT2, ranges in the literature from 13-27%\(^2\). Those patients have an increased chance of a cure by means of radical prostatectomy only. Also, the 5-year disease specific survival rate varies from 85-100%\(^3\). An additional benefit of surgical treatment is the prevention of local complications that relate to the tumor but also to the fact that it is easier to follow up and diagnose relapse in comparison to radiotherapy.

Pre-operative hormonal therapy, despite the fact that it improves pathological - anatomical parameters, such as positive surgical margins, does not affect biochemical or clinical progress of the disease and does not improve survival rates\(^4\). The EORTC 22911 survey presented a distinct survival benefit without disease progress and with improved local control of the disease in patients with positive surgical margins or PT3 disease,
when radical prostatectomy was combined postoperatively with radiotherapy\textsuperscript{23}. In a recent study\textsuperscript{17}, the 5-year, 10-year and 15-year disease-free survival and disease specific survival incT3 disease in patients who had undergone radical prostatectomy, where the majority received adjuvant radio- or hormone- treatment, were 85%, 73% and 67%, and 95%,90% and 79%, respectively. Radical prostatectomy is an option even to high risk patients with locally advanced disease, without increasing morbidity\textsuperscript{17}. A recent study from the USA showed that patients submitted to radical prostatectomy for cT4 disease, had an improved survival rate in comparison to those who received radiotherapy or hormonal therapy as monotherapy, and similar survival rates to those who received combined therapy (RT and HT)\textsuperscript{24}.

Despite many reports in the literature, where survival rates of radical prostatectomy with or without additional treatment, are comparable to those of combined therapy, more randomized prospective studies are required to compare surgical treatment to the combination of radio- and hormonal therapy. The latter is considered by many as the treatment of choice to manage locally advanced prostate cancer. This was reinforced by the EORTC 22863 survey, showing that 5-year disease free survival improved from 79% to 94% and overall survival improved from 62% to 78% when combined treatment was utilized\textsuperscript{23}.

Hormonal therapy contributes to improved results of radiotherapy by suppressing or probably eliminating the latent systematic disease. Moreover, the above combination seems to have additional effects on local control with the promotion of apoptosis in various clone cancer cells\textsuperscript{24, 25}. In our opinion this provides another advantage of surgical removal of the affected organ in cases of locally advanced prostate cancer. Removal of these different cancer cell clones possibly changes the natural progress of the disease, combined when necessary with adjuvant radio- or even hormonal- therapy. This should constitute a subject of study in further research, which will compare radical prostatectomy, supplemented when necessary with radio- or hormonal- therapy, with the combined treatment for the management of clinically locally advanced prostate cancer.

In the present study, all the prostate cancer cases underwent perineal prostatectomy, and as a result the comparison between perineal prostatectomy results and retropubic prostatectomy was not possible in patients within a single centre.

However, comparison with published results from centers experienced in retropubic prostatectomy may lead to safer conclusions regarding the effectiveness of the two treatment approaches. Also, despite the fact that pre-surgical selection of patients participating in similar clinical surveys is appropriate, long-term experience in the particular technique and the volume of patients that underwent surgery have led us to the conclusion that –preoperative selection is not mandatory when perineal prostatectomy is applied, and actually the non-necessity of the preoperative selection should be considered as an important advantage of perineal prostatectomy in comparison to retropubic prostatectomy.

Until the publication of results from further studies, modern data, from both the literature and also from our study show that radical prostatectomy, combined when necessary with radiotherapy or hormonal therapy, has results comparable to those of combined therapy whilst avoiding localized complications related to the tumour.

Improvement of quality of life is the result. The avoidance of morbidity related to the surgical procedure is also of great importance, something
which is also shown by our results with perineal access, as also occurs in localized disease. The low rate of positive surgical margins in our study, relative to that of the international literature\textsuperscript{28-32}, is attributable to the fact that perineal access allows the affected organ and the extent of neoplasms to be removed in total without dissection of the prostate.

**Conclusion**

Radical perineal prostatectomy is a safe option for well-informed patients with clinically diagnosed, locally advanced prostate cancer. The combination of the technique, when necessary, with adjuvant radiotherapy and hormonal therapy contributes to better control of the disease with lower morbidity and maintenance of good quality of life.

Despite the fact that there was no strict pre-operative patient selection there were comparable results to those in patients with clinically localized disease that underwent similar surgery, not only relating to postoperative complications but also to positive surgical margins and urinary incontinence. The markedly low rates of preservation of erectile function are a result of local tumor extension to neurovascular tissue blocks unilaterally or bilaterally. The latest imaging methods of detailed representation of localized tumor extension may also further increase chances of preservation of neurovascular bundles and increase as a result the rates of erectile function maintenance.

More prospective, randomized studies are required to compare surgery with other methods of treatment, but also to compare various different surgical techniques between themselves, in relation to oncological outcomes and complications, and patient quality of life for those patients with clinical locally advanced prostate cancer. It appears that radical perineal prostatectomy, although it remains the oldest form of surgical access to the prostate, remains a relevant choice in the face of new challenges in modern oncological surgery. This is verified by the low rates of positive surgical margins and complications, and also by the satisfactory functional results relative to those of other surgical approaches in the existing literature.

**Περιλήψη**

Λειτουργικά και ονκολογικά αποτελέσματα της ριζικής περινεικής προστατεκτομής στην αντιμετώπιση του κλινικά προχωρημένου τοπικά καρκίνου προστάτη. Η Επιτελεία της ουρολογικής κλινικής του 401 ΓΣΝΑ

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**Εισαγωγή.** Η ριζική προστατεκτομή θεωρείται ως η θεραπεία εκλογής στον εντοπισμένο καρκίνο του προστάτη. Τα τελευταία χρόνια πληθάνουν οι βιβλιογραφικές αναφορές που υποστηρίζουν πως η χειρουργική αντιμετώπιση έχει θέση στην αντιμετώπιση της, τοπικά, προχωρημένης νόσου. Σύμφωνα με τις οδηγίες της Ευρωπαϊκής Ουρολογικής Εταιρείας, η ριζική προστατεκτομή θεωρείται προσαρτική (optional) επιλογή σε καλά επιλεγμένους ασθενείς με, τοπικά, προχωρημένη νόσο. Σκοπός της παρούσας εργασίας είναι να αναδείξει τον ρόλο της περινεικής προσπέλασης σε ασθενείς με, τοπικά, προχωρημένο καρκίνο προστάτη.

**Υλικό και μέθοδος.** Μεταξύ 1993 και 2012, 627 ασθενείς με καρκίνο προστάτη υποβλήθηκαν σε ριζική περινεική προστατεκτομή. Από τους ασθενείς αυτούς 83 έχουν κλινικά,
τοπικά, προχωρημένη νόσο. Συγκρίναμε τη μετεγχειρητική πορεία και τα πρώιμα ογκο-
λογικά αποτελέσματα μεταξύ των δύο ομά-
δων.

Αποτελέσματα. Δεν παρατηρήθηκε διαφορά
όσον αφορά στο μέσο χειρουργικό χρόνο, την
απώλεια αίματος, την παραμονή στο νοσοκο-
μείο και τη διάρκεια καθετηριασμού μεταξύ
tων δύο ομάδων. Δεν υπήρχε στατιστικά ση-
μαντική διαφορά στις μετεγχειρητικές επι-
πλοκές και 2 διερχειρητικές τρίγωνες ορθού
στην ομάδα της τοπικά προχωρημένης νόσου
αποκαταστάθηκαν σε πρώτο χρόνο, επιπλο-
ωτικώς. Στην ομάδα της τοπικά προχωρημένης
νόσου υπήρξε παθολογοανατομική υποστα-
διοπήγη στο 17,3% των περιπτώσεων. Το
99,8% διατήρησαν την εγκράτεια τους και το
36,1% την στιμετή τους λειτουργία έναντι 100
και 62,5% στην ομάδα της εντοπισμένης
νόσου. Δεν υπήρξε στατιστικά σημαντική
dιαφορά στην ειδική της νόσου επιβίωση
μεταξύ των δύο ομάδων.

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