Differences and commonalities in the management of locally advanced prostate cancer: results from a survey of oncologists and urologists in the UK

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OBJECTIVE
To determine the management practices used by UK oncologists and urologists for patients with locally advanced (non-metastatic) prostate cancer.

METHODS
Using a postal questionnaire, 155 practising specialist oncologists and urologists were surveyed in the UK. Their views were sought on a multidisciplinary approach to the management of locally advanced prostate cancer and their current management practices.

RESULTS
Over half of respondents recognized the need for both oncologists and urologists to take the lead in management decisions, but almost as many still expected the sole responsibility to lie within their own speciality. Radical radiotherapy (RT) was considered the current optimum treatment by most respondents, but 22% of urologists thought that radical prostatectomy was optimal. Most responders would use luteinizing hormone-releasing hormone agonists as neoadjuvant and adjuvant to RT but there was significant variation in the favoured duration of treatment of these drugs, and in the dose of RT.

CONCLUSION
This survey suggests that there are still wide variations in the management practices for locally advanced prostate cancer in the UK, and between urologists and oncologists. Improved consensus guidelines are required.

KEYWORDS
oncologists, urologists, locally advanced prostate cancer, survey, UK

INTRODUCTION
In the UK, prostate cancer is the most common form of cancer in men and, after lung cancer, is the second most common cause of cancer-related death for men, accounting for 14% of male cancer deaths [1]. Among men with prostate cancer, about a third present with locally advanced, non-metastatic, stage T3/T4 disease. The term 'locally advanced' prostate cancer (LAPC) could be defined purely in terms of the measurable anatomical extent of the tumour. This would include TNM stage T3 (tumour extending to the periprostatic area or in to seminal vesicles), T4 (tumour invading the external sphincter, bladder neck, rectum, levator ani muscles or fixed to pelvic side wall) or N1 (any local T stage associated with pelvic lymph nodes) but with no evidence of distant metastases, M0 [2]. For men with LAPC there is little consensus on the most appropriate treatment approach. There are several possible treatments, including watchful waiting, radiotherapy (RT), radical prostatectomy (RP) and hormone therapy (HT) either alone or combined, but the precise combination, intensity and timing of treatment are still debatable. Furthermore, there are increasingly many specialists involved in treating patients with prostate cancer, especially urologists and oncologists, and patients need to be allowed to contribute to treatment decisions.

To give some guidance to multidisciplinary teams (MDTs) managing all stages of prostate cancer, the British Uro-oncology Group (BUG) together with the BAUS Section of Oncology and the British Prostate Group (BPG) recently developed an MDT guidance document [3].

BUG was established in 2004 to address the needs of clinical and medical oncologists specialising in urology. The structure of oncology services is different in the UK from many other countries, in that clinical oncologists are specialists in all types of RT treatments as well as chemotherapy, HT and novel treatments. The overriding aim of the organization is to provide a networking and support forum for discussion and exchange of research and policy ideas, and ultimately to advance the education of oncologists involved in the clinical care of patients with urological cancers, to improve the identification, diagnosis and treatment outcomes of disease. The BAUS Section of Oncology represents urological surgeons managing all stages of urological cancers.

To date, the impact of the BUG/BAUS/BPG guidance on clinical practice is unknown and will be dealt with in a separate report. We conducted a survey of the members of BUG and the BAUS Section of Oncology to ascertain the practices used by UK oncologists and urologists for managing patients with LAPC. Specific aspects that were surveyed included: the levels of referral and differences across the UK and between urologists and oncologists; how effectively the MDT approach is being adopted; and the key areas of commonality and differences in the way that LAPC is treated; we present the results of this survey.

METHODS
A postal questionnaire-based survey of practising urological oncologists and
urologists was conducted in the UK. The questionnaires were sent to the 89 oncologists registered on the BUG database at that time, and 150 randomly selected urologists from the BAUS Section of Oncology database. The questionnaire was designed to establish the management practices used by oncologists and urologists for patients with LAPC. Practitioners were provided with a clinical case study and questions elicited the type and duration of treatment used (Appendix). Oncologists were also asked to give a RT schedule to include total dose, number of fractions and duration of treatment. Completed questionnaires were returned to BUG by fax. All data were entered into a database and descriptive statistics were used to analyse the findings.

RESULTS

In all, there were 155 completed responses; 62 oncologists (response rate 70%) and 93 urologists (response rate 62%), with an overall response rate of 65%. Of these, one oncologist and one urologist stated that they were not treating patients with prostate cancer and, as such, were excluded from further analysis. Thus, 98% and 99% of oncologists and urologists, respectively, were actively treating patients with prostate cancer. Unless otherwise stated, the results presented here are based on the responses of 61 oncologists and 92 urologists.

Overall, the oncologists had more referrals for prostate cancer annually, including locally advanced disease, than the urologists, but both groups treated significantly many patients per year (more than one per week) (Table 1).

Question 3 (see Appendix) asked for a definition of LAPC, and virtually every response differed. There were varying combinations of TNM staging, Gleason score and other pathological features, and pre-treatment PSA level. This suggests a need for clearer definitions of LAPC and reflects the fact that current management is more likely to be influenced by individual pathological and biochemical risk factors in combination with anatomical stage, as the vast majority of respondents included these factors as part of their definition, rather than TNM staging alone. The concept of risk groups and algorithms to assess risk have been described by several authors, including D’Amico et al. [4], who classified high-risk patients as stage T2c or greater or with a PSA level of >20 ng/mL, or Gleason score ≥8.

Furthermore, it appears that in clinical practice, the roles of oncologists and urologists are not clearly defined (Fig. 1). Most respondents were in agreement that both should play a leading role in managing patients with LAPC, but agreement to this concept was higher amongst responding urologists than oncologists (78% vs 54%). Both specialities, but especially oncologists, felt that they do, and should, take primary responsibility more often than the other speciality (Fig. 1) and this was reflected by 41% of oncologists stating they should take primary responsibility, as opposed to 17% of urologists. These differences highlight the continued need for multidisciplinary working, but also show that for many centres, this is already accepted standard practice.

The remainder of the responses outlined in this report refer to the management of a hypothetical case of anatomical locally advanced, high-risk prostate cancer presented in the questionnaire (Appendix). The results shown in Fig. 2 suggest that in the UK, oncologists and urologists use different management approaches for patients with LAPC. For example, RP was suggested by 22% of urologists but by no oncologists. Several respondents indicated ‘hormone mono therapy’ but also selected either ‘RP’ or ‘radical RT’, and no respondent selected hormone monotherapy alone. Due to these
contradictory answers some of the data might represent >100% of respondents.

No respondents recommended a policy of watchful waiting or hormone monotherapy alone for this case. Radical RT was identified as the treatment of choice by most respondents, with all oncologists and 77% of urologists advising this therapy (Fig. 2). For those who elected to treat with radical RT, 97% of oncologists and 92% of urologists stated that they would initially treat with neoadjuvant HT (Fig. 3). The commonest choice of agent was an LHRH agonist, with 82% of oncologists and 72% of urologists, respectively, selecting this type of HT.

The use of adjuvant HT (Fig. 4a) was also commonly recommended by oncologists, with 93% of respondents stating that they would recommend further therapy after completing RT. This contrasted with the replies from urologists, where only 49% suggested adjuvant HT. The most frequent choice of hormonal agent was again an LHRH agonist, recommended by 72% of oncologists and 18% of the urologists who elected to treat with adjuvant therapy. Some respondents, 18% of oncologists and 8% of urologists, elected to treat with an adjuvant antiandrogen. There was a variation in the duration of adjuvant HT that was advised, but 31–36 months was the commonest recommendation from both groups, 51% and 40% of oncologists and urologists, respectively (Fig. 4b). The range of duration of adjuvant HT recommended was 0–6 months (4% of oncologists and no urologists); 7–12 months (4% of oncologists and no urologists); 13–24 months (18% of oncologists and 37% of urologists); ≥37 months (4% of oncologists and no urologists) and indefinite (4% of oncologists and no urologists). Some respondents (19% of oncologists and 23% of urologists) stated that they would use an alternative duration of adjuvant therapy to those specified in the survey, but did not indicate for how long they would continue this treatment.

The doses and fractionation schedules of RT recommended by oncologists for this patient with LAPC are shown in Table 2 (most common fractionation and fractionation schedules recommended only once by one oncologist). The differences in fractionation schedules are partly due to some variation in fraction size. In some centres hypofractionated regimens are used, where fewer larger fractions of RT are delivered over a shorter period. These schedules are calculated to have a smaller but equivalent total dose to the conventional 2 Gy/day schedules. However, generally these results show a wide variation in practice and reflect that there is no optimum recommended dose or fractionation schedule for RT for LAPC. However, there is evidence that dose escalation might be of benefit, as discussed below.

The survey finally asked for the respondents opinion on future trends in the management of LAPC (Fig. 5). Most of the oncologists and urologists (67% and 66%, respectively) were in agreement that the use of adjuvant HT will increase in the future. There was also agreement that RP could be increasingly important in the therapeutic options, with
30% of oncologists and 38% of urologists stating that they anticipated an increase in this treatment.

DISCUSSION

This survey of UK urologists and oncologists highlights some of the areas of consensus and some of the areas of disagreement in the management of men with LAPC. A proportion of urologists stated that RP is currently the optimum treatment for LAPC (although no oncologists responded in this manner). RP has traditionally been reserved for cases with a low risk of significant extraprostatic spread. There is increasing evidence that when surgery is used for those with high-risk features the addition of adjuvant therapy might increase control or survival [5,6]. Messing et al. [5] showed that in men with nodal spread and treated by RP the 10-year survival was significantly increased by adding adjuvant castration-based therapy. The European Organisation for Research and Treatment of Cancer (EORTC) 22911 study [6] showed a significant improvement in clinical progression-free survival for men with pT3 disease treated with adjuvant RT after RP. The more traditional recommendations are that patients with this stage of disease should be treated first with external beam RT (EBRT) with or with no HT, or HT alone [3]. However, there would appear to be some consensus between oncologists and urologists that RP will be used increasingly in the future for men with LAPC perhaps as part of a combined approach.

Overall this survey suggests that currently in the UK most oncologists and urologists would advise a combination of radical RT and HT for managing locally advanced disease. Data from clinical trials suggest that this combination is more effective than RT alone in this patient group. Several studies using different timings and duration of HT showed an increase in overall and progression-free survival with the use of combined therapy.

Neoadjuvant HT in the form of LHRH agonists before definitive RT is commonly used by UK oncologists. There are advantages in that this can cause on average a 25–50% cyto reduction of the prostate, and potentially allow smaller fields of RT to be used, with sparing of the rectum and bladder [7,8]. There are reports that there might be a sensitising effect between HT and RT [9]. There are several theories as to the mechanism for this, including that the reduction of tumour bulk improves oxygenation and therefore increases radiation sensitivity [10]. There is also clinical evidence to support this treatment approach.

The Radiation Therapy Oncology Group (RTOG) 86–10 study [11] investigated the addition of HT (goserelin and flutamide) for 2 months before and during RT compared with RT alone for men with LAPC. At a median

**FIG. 4.** The use (a) and duration (b) of adjuvant HT combined with radical RT for the optimum management of patients with LAPC.

A. Percentages are based on the 100% (61) of oncologists and 77% (71) of urologists who answered radical radiotherapy

B. Percentages are based on the 93% (57) of oncologists and 49% (35) of urologists responding radical radiotherapy who indicated adjuvant hormones as optimal management
of 6.7 years of follow-up (8.6 years for surviving patients) there was a significant improvement in disease-free survival and in overall survival for the subgroup with Gleason grade 2–6 disease. Adjuvant hormone manipulation was also commonly advised as combined therapy for LAPC, although there was some variation in the timing and duration of therapy. There is evidence for this treatment approach from several large randomized studies in LAPC. The EORTC 22863 trial [12] evaluated the effectiveness of adjuvant therapy with goserelin 3.6 mg, initiated at the onset of RT and continued for 3 years. Results reported after a median follow-up of 5.5 years showed an improvement in overall survival (78% vs 62%, \( P = 0.001 \)) and disease-free survival (74% vs 40%) in favour of immediate adjuvant HT, as opposed to RT alone with HT at relapse. This study would appear to be influencing treatment decisions amongst clinicians in the UK, as this was the most commonly suggested schedule in the survey.

Further data are available from the RTOG 85–31 study [13], where in all 977 patients were randomized to receive either pelvic RT plus goserelin 3.6 mg (started during the last week of RT, to be continued indefinitely every month or until relapse) or RT alone (goserelin started at relapse). At a median follow-up of 7.6 years, adjuvant goserelin significantly improved absolute survival compared with RT alone (estimated 10-year survival rate, 49% vs 39%; \( P = 0.002 \)). The largest benefits were in the subgroups with high Gleason grades [8–10].

Data from the RTOG 92–02 study [14] also support the use of adjuvant HT; in that study patients were randomized after neoadjuvant therapy (goserelin and flutamide for 4 months before and during RT) and radical RT, to goserelin 3.6 mg for 2 years after completing RT, vs observation. Results reported at a median follow-up of 5.8 years showed that long-term (neoadjuvant, concomitant and adjuvant) goserelin provided significantly better disease-free survival than short-term (neoadjuvant and concomitant) therapy. There was a significantly longer overall survival in patients with baseline Gleason scores of 8–10. There is strong evidence for the use of combined treatment with LHRH agonists, but the optimum duration of adjuvant therapy is uncertain and future studies are needed to clarify this [3].

Some respondents stated that they would advise an antiandrogen for adjuvant HT after RT. Data from the third analysis of the Early Prostate Cancer Study [15] showed that bicalutamide adjuvant to RT significantly improved overall survival compared with RT alone (hazard ratio 0.65; \( P = 0.03 \)) for men with LAPC at a median follow-up of 7.4 years. This represents the first evidence of a significant overall survival benefit for any HT not based on castration and given as adjuvant treatment to patients with prostate cancer. There can be advantages for individual men with the different side-effect profiles between these types of HT.

There was a large variation in radiation doses suggested in the survey, reflecting that the optimal technique and dose of RT for LAPC has yet to be determined. The trend was towards dose escalation and there is evidence that for prostate cancer, increased radiation dose is associated with increased cancer cell death. However, the traditional two-dimensional technique of treatment planning and delivery is limited by the normal tissue toxicity of the surrounding structures (bladder, rectum and bowel), such that the dose that can be safely delivered to the prostate by EBRT is 65–70 Gy [16]. New technological advances have improved the precision of EBRT and have permitted the delivery of higher doses. The use of three-dimensional conformal RT approach has allowed doses to the whole prostate to increase to 78 Gy [17]. More recently, intensity-modulated RT, an advanced form of conformal RT, has enabled doses of >80 Gy to be delivered safely with minimal toxicity [18].

The evidence of benefit from these higher doses was shown in a clinical study by Pollack et al. [17], where patients with prostate cancer were randomized between doses of 70 and 78 Gy. The freedom-from-failure rates at 6 years were 64% and 70% \( (P = 0.03) \) in favour of the 78 Gy group. Increasing the dose to 78 Gy preferentially benefited those with a pre-treatment PSA level of >10 ng/mL.

In the UK, a pilot study from the Royal Marsden Hospital randomized men to 74 Gy or 64 Gy; patients in the first arm tended to have better biochemical control, with 5-year actuarial control of 71% vs 59% in favour of the 74 Gy arm [19]. This trial has lead directly into the MRC RT01 conformal RT study comparing a standard dose of 64 Gy with 74 Gy. Many UK oncologists contributed to this study, reflecting that 26% have adopted a dose of 74 Gy in 37 fractions over 7.5 weeks as their standard fractionation. Some respondents suggested lower doses of RT and
this might depend on local availability of three-dimensional conformal or intensity-modulated RT delivery to allow dose-escalation. Recent biological data suggest that prostate cancer cells have low proliferation indices and the $\alpha/\beta$ ratio (a radiobiological term describing the shape of the cell survival curve for individual tissues) is lower than for other types of cancer cells [20, 21]. Conventionally, radiobiology states that the $\alpha/\beta$ ratios for tumours are higher than those for surrounding normal late-reacting tissue. Tissues with a lower $\alpha/\beta$ ratio will have more cells killed by larger doses per fraction of RT than tissues with a higher ratio. This means that patients with prostate cancer might have high fractionation sensitivity, and provides a rationale for treating with larger doses per fraction than the conventional 2 Gy. Treatment with fewer but larger fractions is termed hypofractionation. It is possible to calculate the equivalent total dose to give the same efficacy as the longer 2 Gy/dose schedules. There are ongoing studies investigating the use of hypofractionated RT [22] for prostate cancer, which might be a more effective way to delivery RT and with associated reduced toxicity. This approach is reflected in some of the responses, where lower total doses are given in a shorter period but with equal therapeutic intent.

There have been major advances in the treatment of LARC in the last 10 years, which emphasizes the need for urologists and oncologists to work together as part of a MDT for the benefit of the patients, and to ensure that they are being appropriately treated. The final questions in this survey showed that both urologists and oncologists agreed that the management of locally advanced disease will change in the near future. Therefore, to encourage team work and to guide physicians through the emerging data on prostate cancer management, guidance is needed. The BUG/BAUS/BPG guidance [3] aims to achieve this, and the results of this survey will hopefully help to target this guidance to areas that lack consensus. In addition, treatment guidelines would complement the BUG/BAUS/BPG guidance and could help to reach a consensus on the optimum management practices for men with LAPC.

CONFLICT OF INTEREST

Both authors are paid consultants to AstraZeneca.

REFERENCES

3 BAUS, BUG, BPG. MDT [Multi-disciplinary Team]. Guidance for Managing Prostate Cancer, 2005 Guidance Available from Authors
(low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 2002; *52*: 6–13


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Abbreviations: HT, hormone therapy; (EB)RT, (external beam) radiotherapy; LAPC, locally advanced prostate cancer; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; RP, radical prostatectomy; MDT, multidisciplinary team; BUG, British Uro-oncology Group; BPG, British Prostate Group.
APPENDIX

The questionnaire from which the data presented in this paper were derived

Call for Your Points of View on Locally Advanced Prostate Cancer

We are all undoubtedly aware that locally advanced prostate cancer is one of the most challenging treatment areas for us at the present time. We hope that feedback from this short questionnaire will help us all gain a broad insight into current practice in this field and help to shape consistency of management approaches in the future. Responses will remain anonymous, but we would appreciate your completion of your details for general information and in order that we can provide you with an overview of the findings. We would be very grateful if you could complete this questionnaire and fax back to 020 8834 1100.

Chair, British Uro-oncology Group (BUG)
On behalf of the BUG Steering Committee

Name:_________________________________________________________________________
Position/Title:_________________________________________________________________
Hospital/Medical Establishment:_________________________________________________________________
Email:_________________________________________________________________________

Q1. Do you currently treat patients with prostate cancer? (Please tick one box)
   A1  Yes ☐  No ☐
   If the answer is no, please fax back the survey to 020 8834 1100.
   If the answer is yes, we would be grateful if you could answer the following questions:

Q2. Approximately, how many new referrals for prostate cancer do you have per year?
   A2   _____

Q3. How would you define locally advanced prostate cancer?
   A3  ________________________________________________________________________________
   _________________________________________________________________________________________

Q4. Approximately, how many new referrals for locally advanced prostate cancer do you have per year?
   A4   _____

Q5a In your clinical practice, who currently takes the lead responsibility for the management of locally advanced prostate cancer? (Please tick one box)
   A5a    Urologist ☐  Oncologist ☐  Both ☐

Q5b In your clinical practice, who do you think should be taking the lead responsibility for the management of locally advanced prostate cancer? (Please tick one box)
   A5b    Urologist ☐  Oncologist ☐  Both ☐

Q6 CASE HISTORY
The case involves a typical patient with locally advanced prostate cancer as discussed in multi-disciplinary meetings across the country. We appreciate that it may be difficult to answer these questions without multi-disciplinary discussion and obviously consultation with the patient to ascertain quality of life issues and patient preferences which can alter the final management plan. However, we would be grateful if you could answer what you consider to be the optimal treatment for this man at the current time with available evidence.

Please turn over...
Mr Brown is a 61 year-old man found to have a PSA of 17.3 on routine screening. He has no significant urinary tract symptoms or co-morbidities. He is married, works as a bank manager and is potent. Clinical examination reveals a T3a prostate cancer and MRI scan and bone scan show no evidence of nodal or distant metastases. Biopsy of the prostate is positive with 8:10 cores showing Gleason 4 + 4 adenocarcinoma. Prostate measures 45cc. Mr Brown is willing to undergo whatever treatment you suggest.

Please indicate your optimal management for Mr Brown:

i) Active surveillance    Yes ☐

ii) Hormone monotherapy
   - LHRH agonist    Yes ☐
   - antiandrogen    Yes ☐

   Duration of hormone therapy ___________

iii) Radical Prostatectomy    Yes ☐
   a) Neoadjuvant hormone therapy
      - LHRH agonist    Yes ☐
      - antiandrogen    Yes ☐

      Duration of hormone therapy ___________

   b) Adjuvant hormone therapy
      - LHRH agonist    Yes ☐
      - antiandrogen    Yes ☐

      Duration of hormone therapy ___________

   c) Adjuvant radiotherapy    Yes ☐

iv) Radial Radiotherapy    Yes ☐
   a) Neoadjuvant hormones
      - LHRH agonist    Yes ☐
      - antiandrogen    Yes ☐

   b) Total Radiotherapy Dose _____ Gy _____ Fraction _____ days

   c) Adjuvant hormones
      - LHRH agonist    Yes ☐
      - antiandrogen    Yes ☐

   Duration of hormone therapy ___________

v) Other treatment (please specify): _______________________________

vi) Who should take the lead responsibility for the continuing management of the patient?

Oncologist ☐ Urologist ☐ Both ☐

Q7. Finally, we would welcome your views on how you think the management of locally advanced prostate cancer is likely to change in the future.

Q7a Do you think the use of radical prostatectomy will...? (Please tick one box)

A7a Increase ☐ Decrease ☐ Remain the same ☐

Q7b Do you think the use of adjuvant hormone therapy will...? (Please tick one box)

A7b Increase ☐ Decrease ☐ Remain the same ☐

Q7c To what extent, and how, do you think the role of the office-based urologist will influence our practice in the future?

Thank you very much for your time