Salvage therapy of small volume prostate cancer nodal failures: A review of the literature

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Accepted 13 November 2013

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Abstract

New imaging modalities may be useful to identify prostate cancer patients with small volume, limited nodal relapse (“oligo-recurrent”) potentially amenable to local treatments (radiotherapy, surgery) with the aim of long-term control of the disease, even in a condition traditionally
considered prognostically unfavorable. This report reviews the new diagnostic tools and the main published data about the role of surgery and radiation therapy in this particular subgroup of patients.

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Keywords: Nodal relapse; Prostate cancer; PET prostate; SBRT; Radiotherapy; Surgery; ADT prostate; Salvage lymph node dissection; Oligo-recurrent disease

1. Introduction

In patients with rising PSA values after primary treatment of prostate cancer the new imaging modalities allow the identification of patients with an apparently limited burden of local and/or metastatic recurrent disease. In the last decade, the new clinical entities termed “oligometastases” and “oligo-recurrences” have been proposed for this clinical condition and are now largely accepted amongst oncologists [1].

Although systemic therapy is the main therapeutic approach in advanced cancer, investigations suggest that local approaches (surgery, radiotherapy) can offer durable progression-free-survival in these selected groups of patients (“chronic curable cancer”) [1,2]. Traditionally, lymph node recurrent prostate cancer after the primary loco-regional treatment has been considered as an unfavorable situation, and palliative systemic hormonal therapy (Androgen Deprivation Therapy, ADT) remains the golden standard in this population of patients [3,4]. Despite that, once started, ADT should often be continued for a long period (usually until progression, when other hormonal manipulations and/or chemotherapy may be considered) and is related with significant side effects and deterioration of the patients quality of life [5]. Therefore, because of the long natural history of the prostate cancer, local therapies are considered with increasing interest, because of their potential efficacy for long term disease control or, even, cure.

The aim of the present review is to provide a correct definition of oligo-recurrent disease, with a focus on recent advances in imaging procedures for the detection of nodal recurrences. Furthermore, all available salvage treatments for nodal prostate cancer relapses are presented and thoroughly discussed.

2. “Oligometastases” and “oligo-recurrence” in prostate cancer patients: in search of a definition

Modern surgical approaches and the advances in radiotherapy treatment planning and dose delivery allow radiation oncologists (and surgeons) to offer potentially curative treatments also to patients that traditionally candidates only to palliative systemic therapies, possibly at a reasonable price in terms of toxicity.

Even if the terms “oligometastases” and “oligo-recurrence” could be considered as synonyms, they do not represent the same clinical situation, since the status of the primary tumor is not the same. Indeed, oligometastatic patients are those presenting 1–5 metastatic sites and also an active primary lesion, while in the oligo-recurrent status, the primary tumor is cured [6]. On the other hand, if several reports agree on the idea that an oligo-recurrent disease should not present more than 5 lesions, at our knowledge there are no clear indications about the size of these lesions. Usually, trials and studies on oligo-recurrent disease consider a diameter of 5 cm the upper limit to treat an oligo-recurrent disease with ablative doses of RT.

Considering the crucial prognostic role of the local control on the primary tumor [6], it could be easily argued that, in theory, an oligo-recurrent disease is more easily amenable to local therapies applied with curative intent than an oligometastatic one.

Last but not least, the possibility to achieve durable tumor control in clinically evident metastatic sites could be relevant also for long term control of the primary tumor or of other sites of micrometastases, following the “seed and soil” and the “multiple steps cancer progression” theories [7,8], and represents one of the most important reasons supporting the role of focused surgical and/or radiation therapies also in potentially multi-micrometastatic patients.

3. Imaging of lymph-nodes by CT and MRI in patients with relapse of prostate cancer

According to many authors, conventional CT and MRI are approximately equivalent in detecting nodal metastases (LNs) [9]. As it is shown in Table 1, all nodes exceeding a minimal threshold of 6–15 mm could be considered potentially involved [9–11]. It should be noted that the threshold of 6–7 mm that is used in some studies is extremely low, explaining its high sensibility, but also probably influencing the accuracy of the results. Despite that, pathologic reports on specimens of nodal dissections for prostate cancer showed that metastatic deposits could be found in about 25% of normal sized LNs [10,12]. Furthermore, it is well known that also benign conditions could be responsible of enlarged LNs.

Tables 1 and 2 summarize the most relevant prospective trials exploring the efficacy of conventional CT scan [12–17] and MRI [12,17–25] to identify prostate cancer nodal metastases, using a reliable pelvic nodal dissection (PLND) or accurate biopsies as reference tests. The sensitivity values represent the great limit of both the techniques: with values ranging between 25% and 78% for the CT scan and between 0% and 86% for the standard MRI, respectively, with a large number of LNs undetected. Saokar et al. compared the sensitivity of CT and MRI [26]. They concluded that MRI
was significantly more accurate than CT in identifying lymph nodes in the range 1–5 mm.

MRI potential has been increased by the introduction of a new contrast medium and functional sequences. The Diffusion Weighted MRI (DWI–MRI) is a functional technique, based on the reduction of water protons mobility in hypercellular cancer tissues, giving a higher signal compared to the surrounding unaffected healthy tissue \([10,11]\). Studies performed with DWI–MRI are limited and not yet conclusive (Table 2). Eiber et al. \([24]\) performed a comparison between DWI–MRI and standard T2W MRI, concluding that the functional sequences of DWI-MRI were significantly more accurate than size-based criteria to detect LNMs (Table II). Moreover, Mir et al. showed that the fusion of DWI-MRI with standard T2W images improves the identification of pelvic LNs in comparison to T2W alone \([27]\), but these results were not confirmed by Budharto et al. in a prospective histopathology-based evaluation of \(^{11}\)C-choline PET-CT and DWI-MRI for the detection of LNMs \([25]\). Despite its obvious interest, DWI-MRI is still under evaluation.

As described by the leading study of Harisinghani \([22]\), confirmed by several other Authors, MR Lymphangiography (MRL) showed very promising results with sensitivity and specificity rates of 82–100% and 93–96%, that are superior to both standard MRI \([22]\) and modern CT \([12]\). However, MRL with USPIO (UltraSmall Particles of Iron Oxide, Ferumoxtran-10) has been substantially abandoned since marketing authorization for contrast medium is lacking.

A recent meta-analysis about the diagnostic performance of 18F-choline and \(^{11}\)C-choline PET or PET-CT in the nodal staging of prostate cancer showed a pooled sensitivity of 49.2% (95% confidence interval [CI], 39.9–58.4) and a pooled specificity of 95% (95% CI, 92–97.1) \([28]\).

The definition of a PSA cut-off value to refer prostate cancer patients with biochemical failure to \([11C]\)Choline PET/CT scanning would be helpful for the clinical management of these patients. Unfortunately, there is currently no consensus on such a cut-off value. Using ROC analysis in a large sample, Giovacchini et al. found that positive and negative \([11C]\)Choline PET/CT scans could be best

### Table 1

Performances of the magnetic resonance imaging (MRI) in detecting nodal metastases.

<table>
<thead>
<tr>
<th>Authors (year of publication)</th>
<th>References</th>
<th>Number of patients</th>
<th>Inferior threshold (mm)</th>
<th>LNM %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heesakkers et al. (2008)</td>
<td>12</td>
<td>375</td>
<td>8–10</td>
<td>16</td>
<td>34</td>
<td>97</td>
<td>NA</td>
</tr>
<tr>
<td>Lecouvet et al. (2012)</td>
<td>17</td>
<td>100</td>
<td>10</td>
<td>NA</td>
<td>77 (R3) 82 (R4)</td>
<td>95 (R3) 96 (R4)</td>
<td>NA</td>
</tr>
<tr>
<td>Bezzi et al. (1988)</td>
<td>18</td>
<td>51</td>
<td>10</td>
<td>25</td>
<td>69</td>
<td>95</td>
<td>88</td>
</tr>
<tr>
<td>Rifkin et al. (1990)</td>
<td>19</td>
<td>185</td>
<td>10</td>
<td>12.5</td>
<td>4</td>
<td>95</td>
<td>NA</td>
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<tr>
<td>Jager et al. (1996)</td>
<td>20</td>
<td>63</td>
<td>8.5</td>
<td>14</td>
<td>60</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>Perrotti et al. (1996)</td>
<td>21</td>
<td>56</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Harisinghani et al. (2003)</td>
<td>22</td>
<td>80</td>
<td>10</td>
<td>NA</td>
<td>45 (standard MRI)</td>
<td>79 (standard MRI)</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al. (2006)</td>
<td>23</td>
<td>411</td>
<td>8</td>
<td>5.5</td>
<td>27</td>
<td>98</td>
<td>NA</td>
</tr>
<tr>
<td>Eiber et al. (2010)</td>
<td>24</td>
<td>29</td>
<td>6</td>
<td>NA</td>
<td>86*</td>
<td>85</td>
<td>86</td>
</tr>
<tr>
<td>Budharto et al. (2011)</td>
<td>25</td>
<td>36</td>
<td>4</td>
<td>47</td>
<td>18.8</td>
<td>97.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Note:** Inferior threshold: Figure above which a lymph node is considered pathological; % LNM: Percentage of patients with positive lymph nodes histopathologically controlled; USPIO contrast agent: UltraSmall Particles of Iron Oxide (no longer commercially available).

\* Correlation with histopathology in only 10 patients; NA: Not available; R1 and R2: Two different readers.

### Table 2

Performances of the conventional CT scan in detecting nodal metastases.

<table>
<thead>
<tr>
<th>Authors (year of publication)</th>
<th>References</th>
<th>Number of patients</th>
<th>Inferior threshold (mm)</th>
<th>LNM %</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
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<td>12</td>
<td>375</td>
<td>8–10</td>
<td>16</td>
<td>34</td>
<td>97</td>
<td>NA</td>
</tr>
<tr>
<td>Golimbu et al. (1981)</td>
<td>13</td>
<td>46</td>
<td>10</td>
<td>37</td>
<td>30</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>Flanagan et al. (1985)</td>
<td>14</td>
<td>53</td>
<td>15</td>
<td>26.5</td>
<td>50</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Van Poppel et al. (1994)</td>
<td>15</td>
<td>285</td>
<td>6</td>
<td>16</td>
<td>78</td>
<td>100</td>
<td>96.5</td>
</tr>
<tr>
<td>Rorvik et al. (1998)</td>
<td>16</td>
<td>64</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>98</td>
<td>NA</td>
</tr>
<tr>
<td>Lecouvet et al. (2012)</td>
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<td>100</td>
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<td>NA</td>
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discriminated using a PSA cut-off value of 1.4 ng/ml, with a sensitivity of 73% and a specificity of 72% while only 24% of patients with a PSA value below 1.4 ng/ml can have positive PET/CT findings [29]. Krause et al. reported a detection rate by [11C]Choline PET/CT of 36% with PSA levels lower than 1 ng/ml [30], while Vees et al. reported a detection rate of about 50% with a similar range [31]. In a recent study by Picchio et al., a potential role of PET, particularly in patients at high risk of relapse with a fast PSA kinetics, was shown even in presence of low PSA values [32].

The discrepancies reported by authors from different Institutions can be attributed to differences in clinical and pathological characteristics of the samples, and statistical uncertainty derived from small sample sizes.

Also for these reasons, the EAU Guidelines clearly discourage the routinely use of [11C]-choline PET/CT for the early diagnosis of nodal relapses from prostate cancer.

These guidelines underline that the detection rate of [11C]Choline PET/CT appears to depend strongly on PSA levels at the time of diagnosis, pathologic stage at time of initial diagnosis, previous biochemical failure, and older age as recently demonstrated in a cohort of 358 patients with PSA relapse following radical prostatectomy and a mean PSA level of 3.97–6.94 ng/ml at the time of evaluation [29]. Furthermore, the probability of false-positive results in up to 20% of patients has to be considered when interpreting PET results [4].

Summary:

- Conventional contrast enhanced CT and MRI still remain the standard for lymph node relapse detection;
- In this setting, DWI–MRI is interesting, but data about its usefulness are not conclusive yet;
- Despite its diffusion in the clinical practice, [11C]Choline PET/CT, remains object of investigation due to the uncertainty regarding PSA value related to its accuracy.

4. Androgen deprivation therapy

ADT, as systemic therapy, is suggested as an appropriate treatment option for advanced and metastatic disease and it has been largely adopted, despite the fact that conflicting data from non randomized trials are available and that the scientific support for this approach is weak.

Nevertheless, in the case of proven metastatic disease, although not curative, ADT as monotherapy remains the up-front standard treatment. ADT is frequently able to provide very good short-term symptom and biochemical control, before the emergence of castration-resistant clones, when second-line hormonal therapy, novel agents, and chemotherapy with docetaxel are instead suggested [4].

In the pre-PSA era, ADT has primarily been used in metastatic disease, especially for symptomatic patients. In the post-PSA era, ADT has progressively been administered also to metastatic prostate cancer patients with longer life expectancies to maintain biochemical control, often in absence of symptoms or in adjuvant setting after radical treatment, particularly when high risk factors of systemic disease are present [34].

However, the optimal timing to administer ADT in patients with a biochemical failure after radical prostatectomy or a radical course of RT remains controversial. After failure, ADT has been shown to be inadequate to extinguish the entire cancer population, and benefits of the ADT should be evaluated also considering its potential deleterious side effects, especially for long term schedules [35–39]. Indeed, some of these side effects can negatively affect the quality of life, especially in young men, while others may contribute to an increased risk for health age-related problems. In this scenario, ADT in salvage setting could be also delayed until symptoms appearance, or when a measurable lesion, as well as nodal relapses, is clearly detected at imaging.

In this context, even in the absence of well-structured studies, various experiences (mainly in the adjuvant postsurgical setting) showed the possibility to achieve a long term cancer control in selected patients with a minimal lymph node involvement, with the addition of hormonal therapy [40–42], with results which did not differ from those of patients without lymph node metastases [43,44]. Radiotherapy associated to ADT has also been shown in retrospective studies to obtain long term disease control and survival in patients with nodal disease at presentation [45].

The evidence about ADT for the treatment of clinically evident isolated nodal relapses of prostate cancer after primary treatment is instead really scarce. This is somewhat paradoxical, since, to date, the standard treatment for this condition is ADT itself.

On the whole, most information on the use of ADT for nodal involvement in prostate cancer refers to patients given ADT integrated with primary treatment (surgery or radiotherapy) for locally advanced disease and therefore to the adjuvant setting.

There are still no clear evidences of overall and/or clinical disease free survival difference when ADT is immediately added, with the exception of few retrospective data [46] and of a single prospective trial [47], showing a positive significant impact of immediate ADT on overall, disease-specific, and progression-free survival compared to the observation arm, where ADT was deferred until disease progression after the local treatment. However, this positive impact of immediate ADT has not been confirmed in other large retrospective studies addressing this issue [48].

The role of ADT, delivered concomitantly to local therapies (such as RT) in the treatment of node positive patients, was studied in the RTOG 85-31 randomized trial, where early androgen suppression plus RT versus RT and delayed HT were prospectively compared [49]. This study represents the only level 1 evidence trial addressing this issue and showed a positive statistical impact of the RT in this clinical setting, but it included only a relatively small number of patients surgically staged.
Briganti et al. retrospectively analyzed data of 703 nodes positive patients treated after surgery with adjuvant HT plus RT and of patients treated with adjuvant HT alone [46]. After a median follow-up of 100 months, adjuvant RT plus hormone therapy significantly improved outcome of pT2-4, pN1 patients, who had a 2.5-fold higher chance of being free from cancer mortality, with significantly higher cancer specific and overall survivals rates.

The dilemma regarding the selection criteria to identify the N+ patients which should receive ADT plus local treatments and the correct timing in delivering them is a major issue. Indeed, not all node-positive patients seem to have the same progression and death risk. [50,51]. In various experiences, tumor stage, preoperative PSA level, Gleason score before and after RP, pathological tumor stage and DNA-ploidy of a tumor have been indicated as important prognostic factors to guide treatment decision [52]. Roach and coworkers showed that the indications to ADT seem to be stronger when the N+ status is associated with higher Gleason score and more advanced T category [53].

Summary

- ADT remains the standard of care;
- high level evidences about ADT in this clinical scenario are lacking;
- perspective, well structured trials are needed to assess the optimal timing and schedule of delivery;

5. Role of surgery

To date, there are only a few investigational studies reporting the outcomes of patients treated after primary therapy with salvage lymph node dissection (sLND) [54–58] for biochemical recurrence (BCR) associated with evidence of nodal uptake at CT-PET (Table 3). None of these studies compared the oncologic outcome of the surgical approach to the one associated with standard treatments, such as ADT.

Moreover, a distinction should be made in the different types of sLND, as in the different published series different surgical procedures have been proposed [54–60].

The introduction of sophisticated imaging modalities, such as [11C]Choline PET/CT scan, has contributed to the selection of candidates for sLND. However, it should be kept in mind that any available imaging modality might significantly underestimate the presence of nodal metastases at recurrence. Therefore, a substantial number of these patients might be affected by more disseminated disease, even in the presence of solitary or limited nodal uptake at [11C]Choline PET/CT [60,61]. This limitation, together with poor patient
selection, might represent the main reason for the limited durable cancer response of sLND that has been reported in some series. However, it has been hypothesized that sLND might also aim at reducing tumor burden in the possible context of cytoreductive therapy, as proposed for other solid tumors [62]. Even though sLND might not be associated with a durable response over time, tumor load might be decreased and further cancer progression might possibly be delayed. Delaying further cancer progression with surgery might represent a significant endpoint for some men with clinically recurrent prostate cancer who have been previously submitted to several therapies, since few treatment options are available for them. In addition to decreasing tumor volume, it might be speculated that this new surgical option might also aim at postponing the delivery of ADT in a proportion of selected patients, therefore reducing the exposure to such systemic therapies that are not devoid of significant side effects [63]. This should, however, be balanced with the potential side effects of sLND.

Rinnab et al. evaluated, in 15 patients with [11C]Choline PET/CT positive nodes patients, the oncologic outcome after surgery. Authors concluded that, despite the potential of the [11C]Choline PET/CT in detection of lymph node metastases when rising PSA occurs, the benefit that can be achieved through [11C]Choline PET/CT and subsequent salvage lymph node dissection is rather small [54].

Recently, Rigatti et al. published the largest prospective series with 72 patients treated with pelvic/retroperitoneal sLND [58]. The authors found that PSA at surgery (<4 ng/ml), time to biochemical relapse (<24 months) and negative lymph nodes at previous RP were independent predictors of PSA response to surgery. The 5-year BCR free survival, clinical recurrence and cancer specific survival rates were 19%, 34% and 75%, respectively. At multivariable analyses, only PSA >4 ng/ml and the presence of retroperitoneal uptake at the pre-salvage LND [11C]Choline PET/CT represented independent preoperative predictors of clinical recurrence. Similarly, the presence of pathologic nodes in the retroperitoneum, higher number of positive lymph nodes and the evidence of a biochemical response (PSA <0.2 ng/ml) assessed 40 days after sLND represented post-operative independent predictors of clinical recurrence after salvage surgery.

These data seem to show that [11C]Choline PET/CT and sLND might be considered for highly selected patients with biochemical relapse of prostate cancer associated with evidence of nodal recurrence. However, only a minority of patients submitted to salvage surgery showed a durable PSA remission, while in the majority of the cases PSA increased after an initial response post surgery. A possible explanation for this might reside on the insufficient selection of the patient cohort included, which might have contributed to dilute the effect of salvage surgery. However, although larger studies are needed to better identify the best candidates for this surgical approach, these preliminary data are hypothesis generating: sLDN seems to achieve the highest success rates in selected patients with limited pelvic nodal recurrence after primary treatment. Moreover, even if in a significant proportion of patients authors failed in showing a durable cancer control, it might be argued that in patients with complete or partial initial PSA response after surgery, the delay of salvage medical therapy (i.e. hormonal blockade) might represent a benefit related to this surgical approach [58].

The role of adjuvant RT after salvage surgery for a nodal relapse remains to be investigated. Jilg et al. reported data about 47 patients operated for a nodal relapse of a previously treated prostate cancer, with 27/47 patients irradiated after salvage surgery. Authors confirm the positive predictive value of the Gleason 6 or less (OR 7.58, p = 0.026), Gleason 7a/b (OR 5.91, p = 0.042) and of the N0 status at primary therapy (OR 8.01, p = 0.011) and the negative predictive value of clinical progression of the preoperative Gleason 8–10 (HR 3.5, p = 0.039) of the presence of retroperitoneal positive lymph nodes (HR 3.76, p = 0.021) and of an incomplete biochemical response (HR 4.0, p = 0.031), but adjuvant RT did not show to have a significant impact on the outcome of the patients [64].

Any salvage “targeted” nodal therapy given in prostate cancer should take into account a potential significant underestimation of nodal recurrence even at [11C]Choline PET/CT [54–58,61]. This is due to the relatively limited spatial resolution of any imaging technique, which might be thus associated with a certain risk of missing micro-metastatic disease. For this reason, another drawback of the surgical treatment resides in the fact that removing only the nodes that resulted positive at imaging might lead to frequent long-term failure rates, but more extensive surgical procedures implies obviously an increased surgical risk.

Summary:

- sLND should be still considered experimental, given the lack of prospective, comparative studies [4];
- the available literature seems to support the surgical approach only in very selected cases of nodal oligo-recurrent prostate cancer;
- the therapeutic value of the surgical approach would be confirmed only after mature data on the efficacy (in terms of overall and cancer-specific survival) and in terms of safety.

6. External beam radiotherapy and stereotactic body radiotherapy for lymph node recurrence from prostate cancer

Radiotherapy is commonly used in the treatment of primary and metastatic prostate cancer lesions [4,65–69]. However, there are very few data on the irradiation of nodal oligo-recurrent disease. Radiation can be delivered with external beam approach (external beam radiotherapy, EBRT) or stereotactic body radiotherapy (SBRT). EBRT is usually delivered to wider volumes using a 3-Dimensional
<table>
<thead>
<tr>
<th>Authors (year of publication) [reference]</th>
<th>Number of pts treated for LN relapse (the whole series)</th>
<th>Local control rate of the series of salvage external beam irradiation (EBRT) for lymph node metastases from prostate cancer.</th>
<th>Median follow-up (months)</th>
<th>Local control rate ± pattern of failure</th>
<th>Overall survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ricchetti et al. (2011) [74]</td>
<td>1 (4)</td>
<td>ADT Helical Tomotherapy Yes PTV 1: positive LN PTV 2: pelvic LN SIB: PTV1: 60 Gy/30fr PTV2:46 Gy/30fr (2–1.53 Gy/fr)</td>
<td>12</td>
<td>No local progression at 12 mos but DM at 16 mos</td>
<td>Alive at 16 months</td>
<td>0</td>
</tr>
<tr>
<td>Jereczek-Fossa et al. (2009) [85]</td>
<td>14</td>
<td>ADT in 7 pts, CHT + ADT in 1 pt SBRT: Linac 7pts – CBK 7 pts PTV1: positive LN 30 Gy/3fr (10 Gy/fr)</td>
<td>18</td>
<td>1 pt died of cardiovascular reason</td>
<td>All pts alive at 22 months</td>
<td>Acute: 0 Late GI G2 1 pt</td>
</tr>
<tr>
<td>Jereczek-Fossa et al. (2012) [84]</td>
<td>b16 (34)</td>
<td>ADT in 75% of pts SBRT (CBK) Yes PTV1: positive LN 33 Gy/3 fr (11 Gy/fr)</td>
<td>22</td>
<td>No local progression, 2 pts with DM and 3 pts with LN relapse No local progression, 5 pts with DM</td>
<td>All pts alive at 22 months</td>
<td>Acute GI: G3 1 pt Late GU: G1: 2pts, G2 1 pt, G3 1 pt Late GI G1 1 pt</td>
</tr>
<tr>
<td>Scorsetti et al. (2011) [79]</td>
<td>1 (12 LN and whole series: 95 pts)</td>
<td>No SBRT (VMAT-RA) No PTV1: positive LN 45 Gy/6 fr (7.5 Gy/fr)</td>
<td>12</td>
<td>Local control; 10/11 LN pts NA</td>
<td>NA</td>
<td>Acute GI G1 3 pts/95pts Late GI G1 1 pt/12 LN pts</td>
</tr>
</tbody>
</table>


Data from the whole cohort of pts.

Conformal Radiation Therapy (3D-CRT) or Intensity Modulated modality (IMRT). IMRT is now commonly employed in radical or post-prostatectomy setting, in particular if a pelvic nodal irradiation is necessary [70,71]. As far as salvage setting is concerned, prophylactic irradiation of pelvic nodal area might play a potential role owing to the risk of occult lymph-nodal metastases [71,33,72,73]. This question is currently addressed in the ongoing trial of the Radiation Therapy Oncology Group (RTOG 05-34) where the patients with a rising PSA after prostatectomy are randomized to pelvic lymph node or prostate bed only irradiation (with or without short androgen deprivation). As far as salvage EBRT is concerned, a MEDLINE search shows only one series of 8 patients and 2 reports of single cases treated using Tomotherapy a particular form of image guided and adaptive IMRT (Table 4) [74–77]. IMRT seems of value in case of irradiation of pelvic nodal chains using simultaneous integrated boost (SIB) approach (with 2 dose levels: lower elective dose to non-involved neighboring lymph node areas and high radical dose to the clinically positive lymph nodes).

SBRT is a novel radiotherapy modality that takes advantage of the technological progress in image guidance and radiation dose delivery, and it is able to direct high ablative doses to small target lesion with acceptable toxicity [78]. It can be delivered with a large number of commercially available systems including those LINAC-based, like volumetric modulated arc therapy [79,80], robotic image guided [80], and other image guided modalities. SBRT seems particularly advantageous for radioresistant tumors, previously irradiated lesions, and small volume tumors. Hypofractionation, which is almost always used when SBRT is chosen, could be of particular value for prostate cancer. Recent in vivo and clinical data suggest that prostate cancer may benefit from hypofractionation as its alpha/beta ratio is lower than that of the rectum and other pelvic organs [81]. Although the data on the alpha/beta ratio of recurrent lesions are not available, a similar benefit can be expected when using this approach for oligo-recurrent prostate cancer.

Again, although SBRT is employed in the management of primary or secondary solid tumors and organ confined prostate cancer [82], few series exist exploring the role of SBRT for the treatment of lymph node recurrence and in particular lymph node recurrence of prostate cancer [83–85]. Small series on the resection of a solitary prostate cancer metastasis (lung, adrenal gland, lymph node lesions) or radiosurgery (stereotactic radiotherapy given in single fraction) to brain metastases from prostate cancer showed good local control, confirming the potential interest of ablative treatments (as SBRT) in oligometastatic and oligo-recurrent prostate cancer patients [85–89]. Three series on the SBRT for isolated lymph node recurrent prostate cancer have been published recently by two groups (Table 4) [79,84,85].

In the vast majority of both EBRT and SBRT patients, the diagnosis of isolated lymph node recurrence was based on the [11C]Choline PET/CT obtained after PSA progression. In some patients recurrent prostate cancer was confirmed by lymph node biopsy.

Obviously, no firm conclusion can be drawn from these small series due to short follow-up, extremely low number of patients, treated with different EBRT and SBRT modalities using heterogeneous fractionation schedules and doses for a variety of limited lymph node recurrences (in same series also metastatic lombo-aortic nodes were included). The majority of patients had heavily pretreated prostate cancer and many received concomitant systemic therapy or were receiving castration resistant disease. Despite these limitations, the results presented in Table 4 suggest that high precision hypofractionated irradiation offers excellent in-filed local control with a very low toxicity profile. The patterns of failure is predominantly out-field and in the SBRT patients recurrence in the neighboring lymph node might be observed suggesting the role of regional lymph node area irradiation, but this should be counterbalanced against potentially higher toxicity (due to larger volumes) and longer overall treatment time (extreme hypofractionation cannot be applied to large volumes). Importantly, a complete biochemical response was observed in almost 60% of the lesions treated with radiation alone [84]. Long treatment-free-interval has also been reported in the same series [84].

Looking at the toxicity rates, Jereczek-Fossa et al. recently published one of the largest series of patients treated with SBRT (Sixty-nine patients, 94 lesions, median SBRT dose 24 Gy/3 fractions) for nodal abdominal relapse from several cancer types (urological, gastrointestinal, gynecologic, and other malignancies) [83]. After a median follow-up of 20 months, SBRT seems to be well tolerated, with only two grade 3 acute and one grade 4 late toxicity events.

These rates compare well with those published by Scorsetti et al. reporting early results about 37 consecutive patients treated with SBRT for abdominal targets (12 of them for abdominal node relapses): both acute and late toxicities reported were minimal [79]. Recent studies have been published reporting dosimetric constraints for SBRT and results of the reported studies seems to show that the respect of these indications allow to obtain very low rates of toxicity, also with increasing doses of RT [90,91].

Summary:

- EBRT and SBRT represent promising non-invasive anatomically-targeted treatment for oligo-recurrent prostate cancer;
- these therapies seem to offer excellent in-field tumor control with very good toxicity profile;
- data regarding large series and/or prospective studies still remain lacking also for EBRT and SBRT;
- the optimal combination of high precision radiation therapy with systemic treatment remains to be investigated.
7. Conclusion

The therapeutic approach to nodal oligo-recurrent prostate cancer patients is still object of debate and no firm conclusions could be drawn. Up to now, hormonal therapies should be still considered the standard of care in this clinical setting. A possible limit to the diffusion of these local approaches could be the lack of accurate imaging techniques to detect the diffusion of the disease. Despite that, a growing interest on the clinical outcomes of the local surgical and not-surgical alternatives has been recently highlighted in the literature. Surgery could be, in very selected cases, a therapeutic option, but the balance between benefits and potential severe side effects should be strictly considered. Radiotherapy and, in particular, SBRT, seems to be a viable therapeutic option in this clinical setting, also considering the low toxicity profile showed in the few published experiences. The correct selection of the patients is crucial in this clinical scenario, in order to identify patients that would really benefit of a local approach in a context of potentially disseminated disease. Moreover, the optimal combination of local therapies with systemic treatments remains to be prospectively investigated.

Conflict of interest

None to be declared.

Funding

No fundings to be declared.

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References


[31] Vees H, Buchegger F, Albrecht S, et al. 18F-choline and/or 11C-acetate positron emission tomography: detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1 ng/mL) after radical prostatectomy. BJU Int 2007;99((6) June):1415–20.


[63] Keating NL, O’Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy:


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