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Patterns of practice of androgen deprivation therapy combined to radiotherapy in favorable and unfavorable intermediate risk prostate cancer. Results of The PROACT Survey from the French GETUG Radiation Oncology group

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1 **Patterns of practice of androgen deprivation therapy combined to radiotherapy in**
2 **favorable and unfavorable intermediate risk prostate cancer. Results of The PROACT**
3 **Survey from the French GETUG Radiation Oncology group**

4
5 **Modalités pratiques la radio-hormonothérapie des cancers prostate de risque**
6 **intermédiaire favorable et défavorable. Résultats de l'enquête Française PROACT du**
7 **groupe radiothérapie du GETUG.**

8
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30
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37

1 **Summary**

2 **Purpose:** The intermediate-risk (IR) prostate cancer (PCa) group is heterogeneous in terms of
3 prognosis. For unfavorable or favorable IR PCa treated by radiotherapy, the optimal strategy
4 remains to be defined. In routine practice, the physician's decision to propose hormonal
5 therapy (HT) is controversial. The PROACT survey aimed to evaluate pattern and preferences
6 of daily practice in France in this IR population.

7 **Materials and Methods:** A web questionnaire was distributed to French radiotherapy
8 members of 91 centers of the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG). The
9 questionnaire included four sections concerning: (i) the specialists who prescribe treatments
10 and multidisciplinary decisions (MTD) validation; (ii) the definition of IR subsets of patients;
11 (iii) radiotherapy parameters; (iv) the pattern of practice regarding cardiovascular (CV) and
12 (iv) metabolic evaluation. A descriptive presentation of the results was used.

13 **Results:** Among the 82 responses (90% of the centers), HT schedules and irradiation
14 techniques were validated by specific board meetings in 54% and 45% of the centers,
15 respectively. Three-fourths (76%) of the centers identified a subset of IR patients for a
16 dedicated strategy. The majority of centers consider PSA >15 (77%) and/or Gleason 7 (4+3)
17 (87%) for an unfavorable IR definition. Overall, 41% of the centers performed systematically
18 a CV evaluation before HT prescription while 61% consider only CV history/status in
19 defining the type of HT. LHRH agonists are more frequently prescribed in both favorable
20 (70%) and unfavorable (98%) IR patients. Finally, weight (80%), metabolic profile (70%) and
21 CV status (77%) of patients are considered for follow-up under HT.

22 **Conclusion:** To the best of our knowledge, this is the first survey on HT practice in IR PCa.
23 The PROACT survey indicates that three-quarters of the respondents identify subsets of IR-
24 patients in tailoring therapy. The CV status of the patient is considered in guiding the HT
25 decision, its duration and type of drug.

1

2 **Résumé**

3 **Objectif de l'étude :** Le cancer de la prostate de risque intermédiaire est hétérogène en
4 termes de pronostic. La stratégie optimale pour le cancer de la prostate de de risque
5 intermédiaire favorable ou défavorable n'est pas encore bien définie. Dans la pratique
6 quotidienne, la décision médicale de proposer l'hormonothérapie reste controversée.
7 L'enquête PROACT avait pour objectif d'évaluer les pratiques en France sur les indications
8 de l'hormonothérapie associée à la radiothérapie.

9 **Matériel et Méthodes :** Un questionnaire électronique a été distribué à 91 centres français
10 membres du Groupe d'Etude des Tumeurs Uro-Genitales (GETUG). Le questionnaire incluait
11 quatre sections: choix de de l'hormonothérapie, pratiques de la radiothérapie, évaluation
12 cardiovasculaire t métabolique avant l'hormonothérapie. Les résultats sont présentés de façon
13 descriptive.

14 **Resultats:** Parmi les 82 réponses (90% de centres), le schéma d'l'hormonothérapie et la
15 technique d'irradiation sont validés lors de Réunions de Concertation Pluridisciplinaires
16 (RCP) dans 54% et 45% des centres respectivement. Trois quarts (76%) des centres ont
17 déclaré identifier des sous-groupes de patients atteints dde cancer de risque intermédiaire pour
18 des stratégies dédiées. La plupart des centres considère une concentration de PSA de plus de
19 15ng/ml (77%) et/ou un score de Gleason de 7 (4+3) (87%) pour la définition du risque
20 intermédiaire défavorable. 41% des centres ont déclaré réaliser une évaluation
21 cardiovasculaire systématique avant la prescription de l'hormonothérapie alors que 61% ne
22 considèrent que l' évaluation cardiovasculaire pour définir le type d'hormonothérapie. Les
23 agonistes de la LHRH sont la forme la plus prescrite chez les patients atteints de cancer de de
24 risque intermédiaire favorable (70%) ou défavorable (98%). Le poids (80%), le profil

1 métabolique (70%) et l'évaluation cardiovasculaire (77%) des patients sont pris en compte
2 pour le suivi des patients sous hormonothérapie.

3 **Conclusion** : A notre connaissance, PROACT est la première enquête sur les critères
4 pratiques de la prescription de l'hormonothérapie dans le cancer de la prostate de risque
5 intermédiaire. L'enquête montre que trois-quarts des centres français identifient les sous
6 groupes de patients atteints de cancer de risque intermédiaire pour adapter le traitement.
7 L'évaluation cardiovasculaire est prise en compte pour décider de l'indication, du type et de
8 la durée de l'hormonothérapie.

9

10 Running title: Practice in ADT and RT for prostate cancer

11 First Author: Y Belkacemi

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1 INTRODUCTION

2 Prostate cancer is the most prevalent male urogenital malignancy in developed countries [1].
3 Androgen deprivation therapy (ADT) has become a cornerstone of treatment in the majority
4 of intermediate risk (IR) and all high-risk patients. In clinical practice, short-term ADT
5 combined with external beam radiotherapy (EBRT) has been validated in several randomized
6 trials [2–6]. Conversely, data in the heterogeneous IR patient population are still controversial
7 [7]. Two controlled randomized trials in IR populations showed that the use of 4-6 months of
8 ADT combined with EBRT resulted in increased overall survival (OS) [2,3]. However, the
9 results of these trials were obtained with different techniques and lower dose levels compared
10 to the standard of care in the modern radiotherapy era. In addition, IR population subsets were
11 defined according to the early 2010-NCCN guidelines [8] or those used by local institutions
12 [9–11].

13 Besides efficacy, ADT is associated with several adverse metabolic effects [12] and cardio-
14 vascular (CV) events [13]. Men with CV risk factors or previous CV events are particularly at
15 high risk to present a new CV event [14,15]. In the latter, the preference of ADT type to use
16 has not been clearly determined to reduce the CV risk [16].

17 In this context, as an academic and private group from the GETUG, we decided to conduct
18 the PROACT (Practice in Radiotherapy and hOrmonotherapy for prostAte Cancer Treatment)
19 survey on pattern and preferences of daily practice of ADT in favorable and unfavorable IR-
20 PCa patients. The hypothesis of the survey was the homogeneity of treatments in terms of
21 EBRT volumes and ADT in IR patients in France.

22

23 MATERIAL AND METHODS

24 The PROACT survey was designed to examine current practice in terms of ADT associated
25 with EBRT in French centers. A web questionnaire was built by the authors (YB, IL and PS)

1 and distributed to the 91 GETUG French radiotherapy affiliated centers. This work was
2 sponsored by the GETUG network. Survey distribution and data collection were done through
3 an email link to the SurveyMonkey® software, keeping data anonymous.

4 The questionnaire included four sections that described: (i) the specialists who prescribe
5 treatments, the multidisciplinary decisions (MTD) validation manner and the type of
6 guidelines used in routine practice; (ii) the way of defining the subsets of unfavorable IR
7 patients and to administer ADT (either short or long course); (iii) EBRT parameters and the
8 choice of duration, sequence and type of drugs; (iv) the pattern of practice regarding CV and
9 metabolic initial evaluation and during patient follow-up. The online survey did not permit
10 partial responses. Results are presented in a descriptive approach.

11

12 **RESULTS**

13 *Centers, decision making and patients*

14 From the 91 GETUG centers that were invited to participate in this survey, 82 responses were
15 obtained (90%). All participating specialists were radiation oncologists and 2/3 (66%) were in
16 public practice. While the global strategy of ADT+EBRT is a MTD and, as such, is
17 systematically decided in multidisciplinary meetings, the type of ADT and the irradiation
18 technique are validated in the framework of dedicated radiotherapy technical meetings in only
19 54% and 45% of the centers, respectively. However, the majority of centers declared that they
20 follow the National guidelines (82%) or participate in clinical trials (75%) (Table 1).

21 Before ADT prescription, participants assessed that prognosis subsets of
22 favorable/unfavorable IR patients were defined according to Zumsteg et al. [7] criteria in
23 three-quarters of the centers (76%) for a dedicated strategy. Only 41% of the centers declared
24 that they perform a systematic CV evaluation (addressing the patient for specialist cardiac

1 evaluation) prior to starting ADT, while 61% considered the CV history/status in determining
2 the type of ADT.

3 Finally, the type of ADT chosen by the physician was mainly influenced by the CV status
4 (80% of centers) and the age of patients (39% of centers). For elderly patients, only 51% of
5 the centers perform oncogeriatric evaluation (addressing the patient for oncogeriatric consult if
6 G8 score is ≤ 14) prior to the ADT+EBRT decision.

7 *Treatments*

8 Half of the 82 centers (50%) declared that they use ADT only in unfavorable IR patients,
9 while the other half use ADT in both IR subsets.

10 LH-RH agonists are used more often, prescribed by 70% and 98% of the centers for favorable
11 and unfavorable IR patients, respectively; in terms of HT duration, a short course (≤ 6 months)
12 is validated in 73% and 66% of the centers for these two subsets of patients, respectively.

13 Regarding EBRT, moderate hypofractionated schedules are used in only 10% and 14% of the
14 centers. Then, 18% and 59% of the centers do pelvic irradiation for favorable and unfavorable
15 IR patients, respectively. In favorable subsets, 40% and 60% of the centers declared using
16 IMRT, delivering 74-76Gy and >76 Gy, respectively. These rates were 54% and 46%,
17 respectively, for the unfavorable subset (Tables 2,3).

18 *Follow-up*

19 During follow-up, metabolic syndrome surveillance, including patient's weight, abdominal
20 perimeter, lipid profile and glycaemia, is performed in 80%, 47%, 70% and 71% of the
21 centers, respectively. Regarding CV investigations during follow-up, the large majority of the
22 centers (77%) declared performing them only in case of CV disease history. In 8% of the
23 centers, systematic CV monitoring is done for all patients under ADT (Table 4).

24

25

1 **DISCUSSION**

2 The NCCN has defined intermediate risk PCa as clinical T2b-c, Gleason 7, or PSA 10-20
3 ng/mL. It is an heterogeneous disease with respect to all outcome endpoints [7,9]. To reduce
4 this heterogeneity, two IR risk groups, either favorable or unfavorable, were individualized
5 [7]. The challenge regarding ADT is to define its benefit/risk ratio in the unfavorable IR
6 patients (with primary Gleason pattern 4, >50% of positive biopsies, or >2 IR factors) with
7 standard dose EBRT and, potentially, in a subset of favorable IR patients with or without
8 dose-escalation.

9 ADT is considered as a cornerstone of treatment in the majority of PCa stages, either for its
10 ability to sensitize cancer cells to x-ray in IR and HR patients or for its potential to halt, or at
11 least, reduce loco-regional progression [17]. It takes advantage of the fact that PCa malignant
12 cells require hormone stimulation for proliferation. Thus, ADT attempts to deny the growth
13 stimulus of tumor cells, potentially impacting on cancer local and distant progression.
14 Indications of ADT are mainly defined according to risk categories in the frame of MTD
15 board meetings and according to international or local guidelines. For IR PCa, guidelines
16 from Europe (European Association of Urology) and USA (American Urological Association
17 and NCCN) recommend combined ADT and EBRT for IR patients [18–20]. The problem of
18 adherence (or not) to guidelines is well known. For example, despite consistent guidance to
19 maintain ADT in castration-resistant prostate cancer (CRPC) patients, a significant variation
20 in clinical practice is observed in different countries. A cross-sectional survey data from five
21 European countries (France, Germany, Italy, Spain and the UK) that included 3,477 patients
22 with CRPC showed that 19% (in the UK) and 45% (in Italy) of patients received
23 chemotherapy alone without ADT. The reasons for these disparities between guidelines and
24 pattern of practice are unclear [21].

25 In the PROACT survey, 82% of the centers follow the national guidelines in routine practice.

1 In addition, ADT+RT indication are defined by MTDs in all centres. However, the type of
2 ADT and EBRT technique, dose and fractionation are fixed during tumour boards in only
3 54% and 45% of the centres, respectively. These data on therapy choice in MTDs are
4 reassuring, knowing the wide heterogeneity of IR PCa patients and the unclear interest of
5 ADT among this subgroup where tailored treatment is needed.

6 Zumsteg et al. [7] suggested IR PCa as an heterogeneous disease that could be divided into
7 two distinct prognostic entities: favorable and unfavorable risk groups with different
8 outcomes that require a risk-adaptive therapeutic approach rather than an uniform approach
9 that cannot optimize the benefit/risk ratio of ADT. More specifically, considering their
10 population of patients with unfavorable IR PCa, they found a 2.4-fold and 4.3-fold increase of
11 biochemical and metastatic recurrences rates, followed by a 7.4-fold increase in specific
12 mortality, despite being nearly twice as likely to receive ADT [22]. In PROACT, only 50% of
13 the centers indicated that ADT is systematic only for unfavorable IR patients, while the other
14 half indicated using ADT in both subsets. Moreover, the majority of centers prescribe short-
15 course ADT either in favorable (66%) or unfavorable IR (73%) patients. Of note, the median
16 duration of ADT was, respectively, 6 and 12 months in both subsets. The 2/3 rate of centers
17 that prescribe ADT+EBRT in favorable IR patients is surprising as, on the other hand, 46% of
18 the centers declared performing dose-escalation of EBRT. Indeed, dose-escalation is still a
19 pending question when ADT is administered, and omitting short-course ADT is a reasonable
20 option for patients with favorable IR PCa in cases of dose escalation of the irradiation
21 schedule in elderly patients or in cases of history of CVs [3,23]. While meta-analyses have
22 demonstrated that both dose escalated EBRT [24] and ADT combined with radiotherapy [25]
23 improved PCa outcomes, there is little evidence supporting the use of DE in patients also
24 under ADT [26]. Neither of the two randomized EBRT+ADT trials that compared 64Gy to
25 74Gy have reported any impact of DE in the IR group. Thus, it is not surprising that the

1 benefit of dose-escalation in patients receiving ADT is still under debate [26–28].

2 Moreover, pelvic irradiation has also been questioned by the PROACT survey. Centers
3 declared including the whole pelvic lymph nodes both in favorable (18%) and in unfavorable
4 IR (59%) patients.

5 In the literature, pelvic irradiation is still controversial. In addition, there are differences in
6 volume delineation proposed by different guidelines [29] and uncertainties regarding patient
7 selection and the impact of pelvic irradiation on outcome. For example, after seven years of
8 follow-up, the RTOG-94–13 randomized trial that included 1323 patients did not demonstrate
9 a clear benefit for pelvic irradiation [28].

10 In clinical practice, the pelvic irradiation decision is based on nodal involvement risk,
11 especially when pathological nodal data are lacking. In general, the risk is calculated using the
12 Roach formula developed in 1994 [30] which yielded best results and is considered as the
13 analytic tool of choice [31] compared to others [32,33].

14 Pelvic irradiation and ADT are considered in cases of treatment intensification in high-risk
15 patients. Conversely, there is no level of evidence for their use in the favorable subgroup of
16 IR PCa. While toxicity has decreased for pelvic irradiation in recent years using modern
17 techniques such as IMRT [34,35], ADT morbidity and mortality should be evaluated
18 regarding the risk/benefit ratio, particularly in favorable IR patients.

19 In terms of metabolic ADT side effects, the diabetes development risk can increase by 44% in
20 the literature [12,36]. In addition, several large population-based studies showed an increased
21 risk of CV events [13,14,36]. In men with risk factors or a history of CV events, the risk of
22 developing new fatal or non-fatal events is particularly high [14,15]. In the PROACT survey,
23 weight (80%), metabolic profile (70%) and CV status (77%) of patients were considered for
24 follow-up under HT. Furthermore, while 41% declared performing a CV investigation prior to
25 HT, only 8% of centers performed it systematically. A limited number (8% and 18%) of

1 centers declared that CV investigations are indicated according to the type of HT (LHRH
2 agonists and antagonists). One study from British Columbia in a relatively elderly population
3 (median age 73y) [37] reported that men with established CV disease (25%) and at least 69%
4 of the subjects without established disease had $\geq 20\%$ risk of developing coronary heart
5 disease prior to ADT initiation. Although one meta-analysis of randomized controlled trials
6 failed to demonstrate an increased risk of CV death among patients who received ADT [38],
7 several retrospective reports showed that ADT administration was an unfavorable prognostic
8 factor for fatal and non-fatal CV events, including myocardial infarction, stroke, and
9 peripheral arterial disease [39,40]. In addition, the use of ADT in patients with pre-existing
10 CV disease is associated with a higher risk of new events [38,41,42].

11 One pooled data analysis looked for differences in cardiovascular morbidity between GnRH
12 agonist and antagonist and found, at one year after treatment initiation, a significantly lower
13 risk of cardiac events in patients treated with LHRH antagonist as compared to LHRH
14 agonists. However, even if the data came from three prospective trials, this was a post hoc
15 analysis that should be considered only as hypothesis generating [43]. Thus, studies
16 comparing different types of HT, such as LHRH agonists vs antagonists, are needed [16].
17 Two multi-center, randomized trials comparing GnRH antagonist and GnRH agonist are now
18 recruiting patients. The PRONOUNCE study's primary objective is time to major adverse CV
19 events in patients with PCa treated with GnRH antagonist or GnRH agonist, while the
20 PEGASUS-EORTC trial's primary objective is progression-free survival in high-risk or
21 locally advanced PCa patients treated with ADT and EBRT; the incidence of cardiovascular
22 events is among the secondary objectives [44,45].

23 In the PROACT survey, 61%, 80%, and 39% of centers declared that the decision of the type
24 of HT to prescribe was guided by the history of CV disease, CV status and age, respectively.

1 Among the different types of ADT, 70% and 98% of centers declared using LHRH analogues
2 for favorable IR patients and unfavorable IR patients, respectively.

3

4 **CONCLUSION**

5 In intermediate- and high-risk PCa, a short course of six months of concomitant and adjuvant
6 HT with radiotherapy improved biochemical-free survival and DFS [46]. However, in the
7 subset of IR patients, HT and EBRT volumes remain under debate.

8 To the best of our knowledge, this is the first survey on the patterns of practice of HT+RT in
9 IR-PCa as defined by Zumsteg. The PROACT survey indicated that three-quarters of the
10 French centers identified a subset of IR-patients for specific management without any impact
11 on EBRT fractionation and/or volume. Only 10% of the centers use hypofractionated
12 schedules and half of these include pelvic nodes for unfavorable IR cases. However,
13 considering recent data on hypofractionation, the number of centers that use hypofractionated
14 schedules could be higher.

15 A short course of HT, using mainly LH-RH analogues, is prescribed for favorable and
16 unfavorable IR patients in more than 75% of the GETUG centers. Furthermore, the CV status
17 of the patients is considered by the majority of centers as the main factor in determining the
18 type of HT to use, despite the fact that there is not a high level of evidence in the literature.

19

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Table 1. Centers and patients

Participation and decision	Criteria	%
Specialists	Radiation Oncologists	96
Institutions	Private facility	44
	Public	66
Decision making	HT-RT in MTDs meeting	99
	Type of HT in MTDs	54
	RT technique in MTDs	45
Clinical trials	Participation	75
Guidelines	National guidelines	82
Patients	Criteria	%
IR patients subsets	Identification as favorable and Unfavorable patients	76
Evaluation prior treatment	Oncogeriatric	51
	Cardio-vascular status	41

IR: intermediate risk; RT: radiotherapy; MTD: multidisciplinary board meetings

Table 2. Androgen deprivation therapy

Treatment – HT	Parameters	%
HT-RT	Only Unfavorable	50
	Favorable and unfavorable	50
Type of HT	History of CV diseases	61
	Influenced by CV status	80
	Influenced by age	39
LH-RH analogues	Favorable IR	70
	Unfavorable IR	98
Short course of HT	Favorable IR	66
	Unfavorable IR	73
Long course of HT	Favorable IR	2
	Unfavorable IR	27
Mean duration (months)	Favorable IR	6 m
	Unfavorable IR	12 m
Concomitant	Favorable IR	55
	Unfavorable IR	76

IR: intermediate risk; RT: radiotherapy; HT: hormonotherapy; CV: cardiovascular

Table 4. Follow-up

Follow-up	Parameters investigated	%
Metabolic syndrome risk	Weight	80
	Abdominal perimeter	47
	Lipid profile	70
	Glycaemia	70
Cardio-vascular investigation	Systematic in all patients	8
	Only if history of CV disease	77
	<i>-Only if LH-RH antagonists</i>	<i>18%</i>
	<i>-Only if LH-RH agonists</i>	<i>8%</i>

Table 3. Radiation therapy

Treatment – RT	Parameters	%
Standard fractionation	Favorable IR	90
	Unfavorable IR	84
Hypofractionated schedules	Favorable IR	10
	Unfavorable IR	14
Technique in Favorable IR	IMRT 74-76Gy	40
	IMRT > 76Gy	60
Technique in Unfavorable IR	IMRT 74-76Gy	54
	IMRT > 76Gy	46
Pelvic irradiation	Favorable IR	18
	Unfavorable IR	59

IR: intermediate risk; IMRT: Intensity modulated radiation therapy